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The Mechanics of Breathing in Acute Severe Croup

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Declaration

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Abstract

Croup is a common respiratory illness that has been recognized for many years. Despite recent advances in the utilization of steroids to treat the condition, it remains a significant cause of morbidity in children. In the developing world it may also remain a significant cause of mortality. Despite comprehensive descriptions of the disease process, its aetiological agents and clinical course, there are very few descriptions of the mechanics of breathing in croup. In addition there are very few methods described of measuring the severity of airway obstruction in patients with croup.

This study of the respiratory mechanics of patients with severe croup set out to:

provide further understanding of the mechanics of breathing in patients with severe croup

assess whether oesophageal manometry using a water-filled feeding catheter could be used in a clinical setting to assess the severity of airway obstruction in patients with severe croup

measure the responses to nebulized adrenaline in severe croup and consider how clinical scoring systems for croup compare with objectively measured airway obstruction.

Chapter 1 Introduction

Chapter 2 Literature review of croup

Chapter 3 Literature review of aspects of the measurement of respiratory mechanics in children, which are relevant to the study of patients with croup

Chapter 4 Description of the patients studied and the methods utilized throughout the studies.

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Chapter 5	A presentation of results from patients and controls with a focus on validation of the methodology
Chapter 6	A comparison of the mechanics of breathing in patients with acute severe croup with normal controls
Chapter 7	A description of the responses of patients with croup to nebulization with adrenaline
Chapter 8	A review of clinical scoring systems of croup, with a particular focus on the parameters used and the practical reproducibility and validity of the scoring system.
Chapter 9	A comparison of objective measures of airway obstruction with the Klein score for the assessment of severity of croup. This focuses on both patients with different clinical scores, as well as data from patients who's clinical scores changed during the course of the studies.
Chapter 10	Conclusions from the studies with recommendations for possible avenues of future research.

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Appendix 4	Source code for programmes used to process the data

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Chapter 1
Introduction

Working at the Red Cross War Memorial Children's Hospital in Cape Town I have been confronted with children suffering from acute severe croup. Many of these children required endotracheal intubation for relief of airway obstruction, and inevitably spent days to weeks in intensive care. Although the mortality from croup is very low the morbidity associated with the condition is high.

On review of the literature it is clear that croup, including a number of variations, has been recognized clinically for many years. The pathology has been clearly documented and the important viral and other aetiological agents have been well reported from different parts of the world. Treatment and outcome has improved markedly over the years. The initial breakthrough was the establishment of artificial airways, initially by tracheostomy and later by endotracheal intubation. Subsequently antibiotics were introduced and more recently nebulized adrenaline and steroids (parenterally, enterally and by nebulization) have been used extensively. Despite these therapeutic advances, very few studies have reported on the mechanics of breathing in croup.

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This thesis therefore set out to:

- Review and discuss the literature pertaining to croup, its management and assessment of severity
- Assess whether the severity of airway obstruction could be measured effectively in a clinical setting using a water filled oesophageal catheter and a facemask with attached pneumotachograph.
- Measure mechanics of breathing using objective parameters (i.e. data which is either measured, or calculated from measured data in an unbiased fashion) in patients with acute severe croup
- Identify features of the mechanics of breathing which are typical and diagnostic of severe croup

Document objectively the responses of patients with severe croup to nebulization with adrenaline

Review the clinically scoring systems that have been developed for use in patients with croup.

Identify clinical features which may be used to assess the severity of croup and use the objective data to assess some aspects of the croup score which was described by Professor Max Klein, and has been used extensively at the Red Cross War Memorial Children's Hospital

The basic measurements used were intra-oesophageal pressure changes using a water-filled catheter - manometer system and air flow at the mouth using a mask-pneumotachograph system. Other values were derived from these measures. In order to perform these measurements, I set up and validated the measurement systems, and wrote and validated computer programs to analyze the measured data. The thesis discusses these methods and the results obtained in different studies.

The initial studies related to the airway mechanics of patients with acute severe croup. Subsequently the responses of these patients to nebulization with adrenaline were measured. Finally clinical and objective data collected during the studies were compared.

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Chapter 2
Croup Literature Review

2.1 Introduction

Croup literature may be subdivided into three broad areas:
Nomenclature and historical perspective
Assessment of croup using clinical and objective criteria.
Treatment of croup

Each of these areas is relevant to a consideration of respiratory mechanics in croup. There are many controversial issues which have arisen within these areas, and assessment of the mechanics of breathing in croup may help to clarify some of the controversies.

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2.2 Nomenclature: A Historical Perspective

"As to the unfortunate word croup, it would be well to expunge it from British scientific medicine, or be careful to employ it unambiguously, which can always be done by the use of a descriptive prefix such as diphtheritic, herpetic, spasmodic etc."(1875) (1)(2)

Since the 19th century the nomenclature of croup has been controversial (2,3). A modern textbook of paediatric respiratory medicine, (4) introduces a chapter on croup with the quote: "Croup syndrome is a sometimes confusing collective term given to a range of symptoms that vary from minimal inspiratory stridor and occasional barking cough to dyspnea, hypoxia and respiratory arrest" (5). A collection of definitions of croup is shown in table 2.1.

Table 2.1: Definitions of Croup

Author	Definition of Croup
Gilbert et al (1941) (6)	"croup may be defined as a state of obstruction to the entrance of air into the lungs as the result of an inflammatory process in the larynx. The inflammation may extend into the lower respiratory tract"
Rabe (1948) (7)	"a disease of the upper respiratory tract characterized by inflammation of the rhinopharynx and downward spread of the infection leading to variable degrees of stenosis of the laryngeal, laryngotracheal, or laryngotracheo-bronchial air passages. The stenosis is due to edema and is aggravated by membrane formation."
Cherry (1979) (8)	"several different respiratory illnesses characterized by varying degrees of inspiratory stridor, cough and hoarseness resulting from obstruction in the region of the larynx"
Couriel (1984) (9)	"An acute clinical syndrome with inspiratory stridor, a barking cough, hoarseness and signs of respiratory distress due to varying degrees of laryngeal or tracheal obstruction"
Rapkin (1985) (10)	"all acute obstructive, infectious and non-infectious upper airway disease."
Baugh & Gilmore (1986) (11)	"infectious croup is a viral or bacterial clinical syndrome characterized by a barking cough, hoarseness and stridor"
Stool (1988) (12)	"is a musical sound that may signal benign disease or a condition which could result in sudden death"
Dorland's Illustrated	"A condition resulting from acute obstruction of

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Author	Definition of Croup
Medical Dictionary 24th Edition 1995	the larynx caused by allergy, foreign body, infection or a new growth occurring chiefly in infants and children and characterized by resonant barking cough, hoarseness and persistent stridor".
Cherry (2007) (13)	"croup is a broad, clinical, diagnostic term used for several different respiratory illnesses that have varying degrees of inspiratory stridor and cough due to obstruction in the supraglottic, glottic and subglottic regions"

The term croup is and has been used interchangeably with other terms including: laryngitis, laryngotracheitis, laryngo-tracheobronchitis etc.

In an editorial entitled "The treatment of croup: Continued controversy due to failure of recognition of historic, ecologic, etiologic and clinical perspectives" Cherry suggested that the three modern events which have influenced the nomenclature of croup are 1) the decline of diphtheria associated with the use of antitoxin 2) the introduction and widespread use of antibiotics and 3) the identification of viral and other non-bacterial infectious agents (8).

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2.2.1 The Diphtheria era

The term croup was first used in medical literature in 1765 by Dr Francis Home of Edinburgh and derived from a Scottish or Swedish term for "stridulous breathing, for crowing or croupy respiration" (2). In 1812 Syer used the term in his treatise: "The croup. Treatise on the management of infants." (12).

During the 19th Century some French authors chose to apply the term croup to all pseudomembranous diseases of the larynx, while others used the term specifically for diphtheria (2). The term "faux croup" was used to describe croup which was characterized by lack of inflammation of the throat and larynx (1). At the same time German authors applied the term "croupal" to all diseases characterized by a

pseudomembranous inflammation (2). English authors used the term croup to include all diseases characterized by stridulous breathing with the exception of diphtheria. Both Bruce (14) and Cumming (3) felt that diphtheria could be clinically distinguished from other causes of stridor although: "the difficulty of diagnosis will lie between herpetic and membranous laryngitis and diphtheritic disease". A distinction was made between diphtheria, membranous or inflammatory croup and false croup (which did not have an inflammatory component (1)). The nomenclature was however a matter of some considerable debate as illustrated by correspondence in both the Lancet and the British Medical Journal during 1875 (1-3,14-32) and which was summarized in an editorial in the Lancet (33,34).

During the era when diphtheria was not treated with antitoxin, Bruce (14), Cumming (3,19) and Rose Cormack (1,2) distinguished between diphtheritic croup and other forms of croup. Billington and O'Dwyer also distinguished between diphtheria and other forms of croup in a text published in 1889 (35) in which the use of the O'Dwyer tube for intubation was described.

In the pre antibiotic era the term tracheobronchitis was introduced in 1912 by Chevalier Jackson (36) when he described a form of tracheobronchitis which he called Influenzal tracheitis. Jackson subsequently described the pathology of acute laryngotracheobronchitis in detail (37) as did several other authors (38-41). Further cases of laryngotracheobronchitis were reported by Baum (42,43). Their descriptions suggest that they were referring to the condition described as membranous croup by Bruce (14,44), Cumming (3,19) and Rose Cormack (1,2)

Reviews of this period included laryngeal diphtheria under the broad category of croup but focussed on the nondiphtheritic conditions.

In 1930 Tolle (45) reported on 344 cases with "croup" and subdivided these into patients with laryngeal diphtheria (212 cases) "catarrhal laryngitis" (126 cases) and other conditions (6 cases). The group of "catarrhal laryngitis" was subdivided into "simple catarrhal laryngitis" (104 patients) and "acute laryngotracheobronchitis" (22 patients). The mortality of the former was 3.8% (all dying of bronchopneumonia)

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while 50% of the latter died. Tolle also suggested that streptococci were responsible for laryngo-tracheobronchitis.

Neffson and Wishik (46) suggested that an aetiological rather than a pathological nomenclature was preferable. They proposed the term "acute non-specific infectious croup" to "denote an acute obstructive inflammation of the larynx, alone or together with the trachea and bronchi, associated with certain pyogenic organisms, particularly streptococci and staphylococci". This disease entity was then subdivided on the basis of pathological findings into acute non-specific infectious laryngitis, acute non-specific infectious laryngotracheitis and acute non-specific infectious laryngotracheobronchitis. This classification was associated with markedly different treatment requirements and outcome (Table 2.2).

Table 2.2: Outcome of patients with acute non-specific infectious laryngitis (46)

	Laryngitis alone	Laryngotracheitis	Laryngotracheo-bronchitis
Number	294	84	22
Tracheostomy	0	7	6
Intubation	0	11	10
Mortality (%)	0.3%	3.6%	68%

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Thus the term laryngotracheobronchitis was initially used to describe a small subgroup of patients with "croup" associated with a very high mortality (Table 2.3). It applied to a severe illness characterized by extensive inflammation of the respiratory tract with associated purulent secretions, airway plugging and clinical features of systemic infection. Although staphylococci and streptococci were frequently isolated from the patients affected, the name was based not on the aetiological agents, but the sites affected by the inflammatory process.

Table 2.3: Mortality of Laryngotracheobronchitis (LTB).

Author	Year	Patients with LTB**	Tracheostomy / Intubation	Mortality (%)
Baum (42)	1924	4	4	100
Baum (43)	1928	24	24	42
Tolle (45)	1930	22	11	50
Gittins (38)	1932	24	15	38
Richards (39)	1933	11	11	64
Neffson & Wishik (46)	1934	22	21	68
Richards (39)	1933	28	23	40
Richards (47)	1938	17	7	41
Brenneman et al (40)	1938	45	41	42
Davison (48)	1940	17	10	11.7
Brighton (49)	1940	27	27	40
Gilbert et al (6)	1941	8	8	88
Rabe (7)	1948	43		15.8

** clinical features of obstruction at the level of the larynx but also extending below the subglottis.

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In 1972 Wesley et al (50) commented that “the reported mortality rate for laryngotracheitis is negligible, but involvement of the lower respiratory tract increased the rate considerably”.

As pointed out by Nelson (51) clinical features of this laryngotracheobronchitis are virtually identical to the "bacterial croup" or "membranous croup" described in the 1980's (52-59). The clinical course of the bacterial laryngotracheobronchitis is much more severe than the viral illness, and may be complicated by airway obstruction, membrane development (with increased risk of obstruction), toxic shock (60) and death. The diagnosis of bacterial croup may however not be straightforward. As pointed out by Isles and Newth (61) “when a child with acute laryngotracheo-bronchitis undergoes tracheal intubation, the secretions are usually copious and

appear “dirty” since the endotracheal tube has to pass through the contaminated oropharynx. Hence, bacteria are frequently cultured from the secretions obtained through the tube. *Staphylococcus aureus* and *Haemophilus influenzae* are both commonly carried in the oropharynx of children, and culture alone in this situation does not provide sufficient evidence that they are pathogens”. They suggested that the presence of pus cells in the tracheal aspirate was essential for the diagnosis of bacterial croup (62).

Rabe (7) also proposed a nomenclature based primarily on presumed aetiological agents with a secondary classification on the grounds of clinical extent of the disease (i.e. extent of inflammation from the larynx down into the alveoli). It is notable that this definition of the condition included reference to the pathology of the nose and pharynx. On the basis of presumed aetiology Rabe divided croup into 3 groups namely diphtheritic, viral and haemophilus. Each group was recognisable clinically, and within each group morbidity was related to the extent of the pathology (e.g. in the viral group mortality ranged from 0.6% in the laryngitis subgroup to 15.8% in the laryngotracheobronchitis subgroup) (63).

In describing "Hemophilus influenzae type B" croup Rabe (64) was building on the work of Sinclair (65) at Yale and included Sinclair's cases in his report. Both described the typical features of the swollen and inflamed epiglottis. The term epiglottitis is attributed to Alden Miller by Nelson (51).

Although Rabe had referred to the category of "viral croup" he had not actually isolated viruses from the group, instead he made the assumption that these were of viral aetiology on the basis of absence of consistent bacteriological findings and the similarity of clinical features to the virus associated laryngotracheitis of chickens (66).

2.2.2 The post antibiotic era

After the introduction of antibiotics, the isolation of viruses from patients with croup (67-69) gave weight to the concept that viral infection was responsible for the disease pattern. Subsequent studies demonstrated the role of parainfluenzae (70-

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73,73), respiratory syncytial, adeno- and rhinovirus (73-75) influenza (76,77), measles and herpes viruses (78) and other viruses (79) in the aetiology of "croup".

Gilbert (80) pointed to a substantial improvement in outcome for patients with nondiphtheritic croup following the introduction of antibiotic therapy, suggesting that bacteria were important in the pathogenesis of "viral" croup. Gilbert also criticized classifications of croup based on infectious aetiology alone. He felt that such a classification grouped together patients with great differences in "pathology, symptomatology and prognosis and ..... treatment". When speaking of the H influenzae type B croup of Sinclair and Rabe he commented: "The sequela of hypoxia that follows the local pathological changes of supraglottic edematous obstructive laryngitis has, in our experience, proved of more clinical importance than general toxic effects caused by the infectious agents."

During this era the clinical picture of croup was generally at the milder end of the spectrum. The full-blown picture of laryngotracheobronchitis as described during the 1920's and 1930's became so uncommon that it was described as a new form of severe croup in the 1980's (see above). The term laryngotracheobronchitis was used as a synonym for viral croup by many authors, and the reported mortality of croup became extremely low.

During investigation of the "new" entity of bacterial croup Edwards et al produced evidence from 2 patients that bacterial croup was the result of bacterial infection superimposed on an underlying viral infection (81). Similar evidence was provided by Naqvi and Dunkle (82), while Conley et al described bacterial tracheitis as a complication of measles (83). Farber and Berg (84) provided evidence that bacterial tracheitis could complicate other invasions of the defence mechanisms such as endotracheal intubation. Bacterial croup was felt to be a secondary complication rather than a primary cause of croup. The organisms involved were primarily *Staphylococcus aureus, Haemophilus influenzae*, and various Streptococci (52-59,84-86) but *Branhamella catarrhalis* (87) has also been isolated.

Other organisms were implicated in the aetiology of croup. Miller et al (88) reported a patient with clinical features indistinguishable from acute viral croup, but from

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whom *Chlamydia trachomatis* was isolated, and who responded rapidly to treatment with erythromycin. Cooke et al (89) reported on a child with symptoms of croup who was found to have *Salmonella virchow* on blood culture

Welliver et al (90,91) showed evidence that patients who developed croup during parainfluenza epidemics had immune responses which differed from other patients who had infection but no croup. They studied 37 infants and children presenting with croup or an upper respiratory illness alone due to parainfluenza virus during the autumn of 1983. Twenty-seven of the patients had croup on clinical grounds, and of those 17 had a history of a previous episode of croup. The study showed that patients with croup had higher IgE responses to parainfluenza virus in nasopharyngeal secretions; increased lymphocyte transformation responses of peripheral lymphocytes to parainfluenza virus antigen and reduced histamine-induced suppression of lymphocyte transformation responses to parainfluenza antigen.

Similarly Zach et al demonstrated lower levels of IgA in patients with recurrent croup (92). Thus the patient immune response to infection may also be important in the aetiology of "viral croup" and recurrent croup. A recent study (93) reported that serum eosinophilic cationic protein (ECP) and IgE levels increase in the acute phase of infection and return to normal after treatment in patients with croup, again suggesting that there may be an allergic component in the responses to viral infections of patients with croup.

Zach et al investigated children who had recurrent croup, showing that children with recurrent croup had similar responses to inhaled histamine as children with asthma, except that some tended to have more changes in the inspiratory limb of flow volume curves (92,94-96). When a group of children who had previously been admitted to hospital with croup were examined 9 years following that admission, the group with recurrent croup episodes were found to have a higher incidence of allergy and airway hyper-reactivity, and higher tendency to subsequent development of asthma (95).

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Hide and Guyer (97) followed up a cohort of 486 children from birth. Thirty one (21 boys and 10 girls) of those patients had recurrent croup and this was associated with a positive family history of allergy.

Thus there is some evidence that a group of patients with recurrent croup may be presenting with manifestations of an allergic diathesis. In these patients the pathological process in the subglottis (or throughout the respiratory system) may be different to those children who had a direct infective response.

In a cautionary article Farmer and Wohl investigated a group of 58 children who had been referred to an otorhinolaryngology clinic for assessment of "recurrent croup", and demonstrated that 10 had gastro-oesophageal reflux disease, 10 had atopy, and 37 had either intrinsic (28 patients) or extrinsic (9 patients) airway abnormalities (98).

Thus over the years the nomenclature of croup has been complicated by the recognition that laryngeal airway obstruction may have a variety of causes, variable clinical courses and may require a wide range of differing treatments. No single classification based on aetiological agents, anatomical distribution of inflammation or clinical features is adequate. For clarity it is important that the advice of Rose Cormack (1,2) be heeded and the term croup be deleted or used with appropriate descriptive addenda.

Recently the terms laryngotracheitis and laryngotracheobronchitis have been used to describe "viral croup". This is inappropriate in view of the history of the term laryngotracheobronchitis which was clearly applied to a severe and extensive bacterial infection of the bronchial tree. It is inappropriate in view of the comment of Rabe (7) that the pathology affects the nose, and pharynx as well as the bronchial tree. It is also inappropriate from a clinical perspective, in that it suggests that inflammation of the larynx, trachea and bronchi is of equal clinical significance and ignores the possible co-existence of alveolar disease or pneumonia. Articles on croup have pointed out that bypass of the laryngeal obstruction alone by tracheostomy or endotracheal intubation relieves most of the airways obstruction in

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severely affected children (99,100) suggesting that the pathology in other areas is not usually particularly important from a clinical perspective.

Table 2.4: Conditions grouped under the heading "croup"

laryngeal diphtheria
viral (predominantly parainfluenzae) infections affecting the glottis and subglottis
epiglottitis caused by H influenzae type B
bacterial infections of the part or all of the laryngo-tracheo-bronchial tree which may be secondary to preceding viral infections or mechanical injury
spasmodic croup which is related to viral infections, but which differs from other viral infections in that the pathology appears to be primarily allergic
other conditions including foreign body aspiration and angioneurotic oedema affecting the laryngeal region

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Despite the above objections to the term laryngotracheobronchitis (LTB), it is unlikely that use of the term will change. In the same way in which the term croup should be used with descriptive addenda, the term LTB should be used with appropriate adjectives, describing the presumed aetiological agents, the site of maximal airway obstruction and the extent of other airway involvement (e.g. the nose).

With the addition of the descriptive terms either "croup" or "laryngotracheo-bronchitis" would be acceptable.

In 2001 Hatherill et al (101) reviewed the findings at microlaryngoscopy of 148 children who had been admitted to the PICU of the Red Cross War Memorial Children's Hospital. Among this group of children there were 15 with laryngeal ulceration and oedema which was compatible with herpetic infection. Sporadic cases had previously been reported by a number of authors (78,102-106), but this was the largest series on record. Six of the children with laryngeal ulceration did not

have any oropharyngeal lesions of herpes, while 18 of 27 children with oropharyngeal lesions did not have laryngeal lesions.

For the purposes of this thesis I will be using the term croup to describe a condition characterized clinically by stridulous breathing; pathologically by inflammation and oedema of the subglottis (although other parts of the respiratory tract may also be involved); aetiologically by viral infections excluding measles and herpes. Patients with diphtheria, epiglottitis, foreign bodies, congenital abnormalities of the airways and secondary bacterial infection of the airways (as manifest by purulent secretions with crusting and plugging of the airways) will be excluded.

2.3 Assessment of Croup Severity

Clinical assessment of croup is difficult (107). The concept of an accurate and reliable clinical scoring system is attractive as it would facilitate the development of clinical management protocols and would provide a tool to measure responses to treatment.

Objective assessment of croup severity is also difficult. Patients at the more severe end of the spectrum have critically narrowed airways, and it is essential that measuring systems do not compromise the patient.

In the following sections I will review first the clinical scoring systems which have been developed and then objective measures of croup severity. A more systematic review of clinical scoring systems and their relationship to objective measurement systems will be provided in Chapters 8 and 9.

2.3.1 Clinical scoring systems

Clinical scores of illness severity are used in a number of ways. Firstly to assess the severity of the disease for research purposes - in the case of croup no clinical score has been comprehensively validated against objective assessments of airway obstruction. Secondly to predict possible outcome, and in the case of croup only the Syracuse score has been validated against the outcome of patients assessed (108).

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Thirdly scores are used as a basis of decision making e.g. whether a patient should be intubated or not. Thus an ideal clinical score should be validated:

> over a range of severity of illness
>
> against an objective measurement of severity of disease at the time of the assessment
>
> against outcome
>
> against its predictive value for predicting appropriate intervention.
>
> for interobserver error (109)

A wide variety of clinical scoring systems for croup have been published and used as tools for the assessment of severity of croup in clinical trials (table 2.5). These scoring systems will be evaluated in more detail in chapter 8. However there is wide variation both in clinical features assessed and the method of scoring for each feature. In addition several scores attributed different values to various clinical features (e.g. in the Westley score, the presence of cyanosis scored 5 points, while the presence of stridor scored a maximum of 3 points).

One clinical score which has been formally evaluated is the "Syracuse croup score". This score was found to be useful, when used in an outpatient setting, to predict which children could safely be admitted to a general paediatric ward in preference to an ICU (108). The score did not however accurately predict which children would require ICU admission. As the study looked at a population of 165 children of whom only 3 were intubated (indications for intubation not given), and the mean and median scores were 5.7 and 5.5 respectively (out of a maximum score of 15), it did not assess the validity of the score for the assessment of more severe croup. Finally the score was only evaluated in terms of the prediction of outcome, and not in terms of prediction of severity of airways obstruction at the time of the test.

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Table 2.5: Clinical scoring systems

Score	Reference	Citations
James	James et al, 1969 (181)	
Ross	Ross et al, 1969 (110)	
Gardner	Gardner et al, 1973 (111)	
Clinical score	Wesley, 1974 (112)	
Downes	Downes and Rafaely, 1975 (113)	Remington and Meakin, 1986 (114)
Taussig	Taussig et al, 1975 (115)	
Westley	Westley et al, 1978 (116)	Fogel et al, 1982 (117), (118)
Fogel modification of Westley	Fogel et al, 1982 (117)	
Syracuse score	Leipzig et al, 1979 (119)	Jacobs et al, 1994 (108)
Klein score (see appendix 1 for details)	Klein, 1986 (120)	
Dyspnoea and Cough score	Kuusela and Vesikari, 1988 (121)	
Modified Westley	Super et al, 1989 (122), Luria et al, 2001(123)	Cruz et al, 1995 (124)
Sivan	Sivan et al, 1990 (125)	
Downes score modified by Waisman et al	Waisman et al, 1992 (126)	
Overall clinical assessment score	Husby et al, 1993 (127) (modification of Westley)	
Kristjanssen	Kristjanssen et al, 1994 (128)	
Nutman (stridor scoring system)	Nutman et al, 1994 (129)	
Geelhoed and Macdonald	Geelhoed and Macdonald, 1995 (130)	

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Croup Severity	Johnson et al, 2003 (131)	
Chan et al	Chan et al, 2001 (132)	

Waisman et al (126) in a study that compared L-Epinephrine with racemic epinephrine nebulisation found that the interobserver variability (between 6 study group members) did not exceed 1 point (in a 10 point score) during the training period or during their actual study. The mean croup scores in the 2 groups were 7.2 and 6.8 (out of a possible 10).

In a research study of patients with mild croup (Westley score between 2 and 9, with median of 4) research assistants and physician investigators rated the croup scores of 12 patients concurrently to measure interobserver reliability. The weighted kappa statistic (±SE) was 0.95 ±0.02, indicating excellent agreement. (133)

The interobserver variability in the assessment of paediatric post-extubation stridor was assessed by Kemper et al (109). Of the parameters assessed by a variety of staff in the 5 minutes following 27 extubations of 25 children less than 15 years of age (median age 7 years) respiratory rate and flaring/retractions were found to be relatively reliable (weighted Kappa statistic (K_W) >.61), while stridor and level of consciousness were only moderately reliable (K_W .40 to .60). Agreement about air movement was no different from that expected by chance alone (K_W < .4).

Geelhoed and Macdonald reported a weighted kappa statistic of 0.85 on scores allocated in retrospect by a blinded observer on values recorded by triage nurses during the trial (vs recorded scores). They had developed their own score for the study (130), with a maximum score of 6 (the average score at the start of the study was 3.8).

Chan et al (132) undertook a large study of 158 (out of possible 478 children with croup) in which each patient was evaluated independently (but within a period of 1 hour before treatment was started). They developed their own score, incorporating elements from reported scores, which had a maximum score of 18. Their patients had a mean score of 3.5, and only 1 patient had an abnormal score for colour, and 2

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an abnormal score for level of consciousness. Interobserver agreement was assessed using Cohen's quadratic weighted kappa, and while the agreement was greater than chance for all clinical signs, the highest agreement (0.4-0.5) was seen for stridor and retractions. Overall the level of agreement was classified as fair to moderate.

Thus although a number of clinical scores of croup severity have been described, and used extensively in research on management of croup none of these scores have ever been validated comprehensively over the full range of croup severity; against objective measures of the severity of airway obstruction; for prediction of the need for a particular intervention; or against clinical outcome of the illness. It is also important to note that the limited studies of reliability of croup scores have shown low interobserver differences when used by a research team for research purposes (126,130,133), but significant differences when reviewed in the context of clinical application (109, 132).

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2.3.2 Objective measurements in croup

Inspiratory and expiratory resistance in a 7.5 year old child with croup was reported by Ingelstedt et al (134) as being higher than normal controls and higher during inspiration than expiration. The resistance was measured from intraoesophageal pressure changes while the patient was breathing through a volume flow regulator, which admitted a constant volume flow of air regardless of the patient efforts. Studies were performed on normal controls and patients who had recently suffered an attack of "pseudocroup" (described as subglottic laryngitis). They concluded that there was no evidence that the airways of patients who had recently had "pseudocroup" were more collapsible than normal, but that the increased inspiratory resistance of croup was related to subglottic oedema. They postulated that dynamic compression of the upper airways occurred as an effect secondary to the subglottic oedema.

Couriel et al (9) reported flow volume loops on 2 patients with croup aged over 8 and 9 years respectively. One patient showed evidence of fixed proximal obstruction, while the other showed evidence of a variable extra-thoracic obstruction. The 8 year old boy showed a marked improvement following inhalation of racemic

adrenaline. As the majority of patients with croup are less than 3 years of age it is difficult to know how relevant this data is to the usual pattern of croup.

The first attempts to quantify severity employed blood gas analysis. These studies showed that hypoxemia was a common feature, and that although arterial carbon dioxide tension rose in severe croup (107,135) the rise occurred late and could not be used to predict outcome.

Arterial pO_2 levels were found to be low in 29 of 35 patients with croup (107), but did not correlate with severity of croup. Similarly Wesley et al (135) studied 31 children with "infective croup" (24 had measles related croup, 5 had laryngeal diphtheria and 2 had viral croup as described by Rabe (63)) and found that 73% of patients had a widened alveolar to arterial oxygen pressure gradient ($PAaO_2$). A review of 29 children (out of 199 children admitted to hospital) with “severe enough croup to undergo monitoring with oximetry” showed that 8 (27%) had an admission oxygen saturation of <90%. There was no correlation between respiratory rate and saturation. Some patients showed a sudden drop in saturation with no associated change in respiratory rate (136). Studies of oxygen saturation following adrenaline nebulization (128) showed no change although there was an improvement in clinical score. Another study showed no changes in oxygen saturation in patients with croup following administration of nebulized adrenaline or chloral hydrate, despite changes in croup score (137)

In a study of 57 patients with viral croup (75% measles), Wesley (112) found that arterial pCO_2 was below normal in patients with mild croup (or in those with "normal air entry"). Patients assessed as having severe airway obstruction had normal arterial pCO_2. Thus pCO_2 measurement was not useful in the prediction of outcome of patients.

Transcutaneous pCO_2 levels varied with the severity of croup (137), however absolute pCO_2 levels were not shown to correlate with croup severity. Again the pCO_2 levels were compared with clinical scores of croup severity and not with any objective measures of airway obstruction.

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Davis et al (138) measured thoraco-abdominal phase angle asynchrony (TAA), air flow and pCO_2 in a group of 6 patients (aged 7 to 13 months) with severe laryngotracheobronchitis (all admitted to PICU, but none intubated) in the acute phase and during recovery. All these patients required inspired oxygen concentration of > 35% to maintain a transcutaneous pO_2 of >55mmHg. They were able to show that as patients improved the pCO_2 dropped, the minute ventilation increased, and the phase angle decreased. Thus the distortion of the chest wall, as measured by TAA, correlated with other measurements of respiratory system function. They did not however correlate these findings with clinical scores or scoring systems.

A larger group of patients with upper airways obstruction were studied by Sivan et al (125). They studied 17 children, of whom 5 had "laryngotracheitis (croup)" and the remainder had post-extubation stridor. In addition to measurements of TAA, they measured tidal flow volume loops, saturation and clinical score using an "acute upper airway scoring system". They measured patients at baseline, and then after nebulization with adrenaline. In this study they were able to demonstrate that adrenaline nebulization was associated with an improvement in peak- and mid-inspiratory tidal flow, ratio of mid-inspiratory to mid-expiratory tidal flow, tidal volume, phase angle and clinical croup score in some patients. The same group validated the technique of TAA in an animal model (rhesus monkey) using varying degrees of fixed inspiratory obstruction (139). In this setting it was found to correlate well with the degree of obstruction. However the TAA changes were not equal over the range of imposed obstruction, with the major changes in TAA occurring in the range of resistance of 0-200cm H_2O/L/s. Although measurement of TAA seems to be a robust tool for assessment of severity of upper airways obstruction, it is not a direct measure of the pressures generated within the thorax. The measurement is not an absolute one, and may be influenced by a variety of factors including the exact positioning of the strips. An additional study has demonstrated that analysis of thoracoabdominal asynchrony may be complex in some patients when signals from the ribcage and the abdomen are not sinusoidal (140). Thus although the technique may be used to demonstrate changes in a specific patient over a period of time, it may have limited use for comparing severity of patients, and even on the same patient on different occasions.

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Oscillometry has been used to assess resistance in convalescent patients with croup (141), but never in patients during the acute illness. This did not reveal patterns of resistance during the respiratory cycle, but only at mid inspiration. This methodology revealed a significant but temporary drop in airways resistance (30%) of 7 of the 8 patients following administration of phenylephrine. However this methodology has never been assessed in acute severe croup, and is not in general use.

Other than intra-tracheal measurements on a single croup patient who had been subjected to tracheostomy (142) intrathoracic pressure changes in croup have not been reported in the literature. Newton-John measured intra-tracheal pressure change in an 18 month old boy who had been tracheostomized for severe croup. On removal of the tracheostomy tube 3 days later, occlusion of the stoma produced clinical signs of severe airway obstruction. Before reinsertion of the tracheostomy, pressures in the trachea were measured and showed inspiratory pressures of -24 to -50 (mean -37) cm H_2O and expiratory pressures of 5 to 15 (mean 11) cm H_2O (142).

Luke et al (143) performed cardiac catheterization on 3 children with severe oropharyngeal airway obstruction. On one of those children, there was marked breath to breath variation demonstrated in both aortic and pulmonary artery pressures of approximately 20mmHg.

Steele et al (144) showed that there was strong concordance between the croup score (Westley) and the pulsus paradoxus (measured non-invasively) both at the time of presentation and following nebulization with adrenaline, in a group of 28 patients with croup. The paper does not quote statistics regarding the croup score, but examination of a figure suggests that croup scores ranged from 0 to 12 with the majority 5 or less. The pulsus paradoxus (mm Hg) varied from 0 to nearly 50 in this group of patients. In addition adrenaline nebulisation was related to a mean decrease in pulsus paradoxus of 7.5mm Hg and a median drop in croup score of 1.5.

Narrowing by 61.3% of the anteroposterior diameter of the extrathoracic trachea during inspiration in croup (145), and 58% reduction in tracheal cross-sectional area

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during inspiration in a patient with laryngomalacia (146) have been shown. Narrowing of the trachea at the cervico-thoracic junction during inspiration in infants with upper airways obstruction has been demonstrated on cineradiography (147).

Thus relatively few studies have documented mechanics of breathing in croup. There are only a few reported studies on a total of approximately 12 patients with croup, in which severity of airway obstruction has been measured. The intra-thoracic pressures that develop during croup have only been reported once, and there are very few studies which have correlated clinical scoring systems with objective measurements of croup severity during the acute phase. Relatively little data is available on the mechanics of breathing in acute severe croup.

2.4 Treatment of Croup

2.4.1 Introduction

Tracheostomy and endotracheal intubation were both used for the treatment of croup during the 19th century. Alberti (148) reviewed the 19th century controversy of tracheostomy vs. intubation, and commented that "there is no doubt, however, that in the last two decades of the 19th century the lives of more children were saved by intubation than by all the tracheostomies performed to that time." Despite this the issue of whether tracheostomy is preferable to intubation remained a point of debate at the end of the 20th century. Endotracheal intubation is probably more commonly used than tracheostomy as the first-line treatment of critical airway obstruction from croup (50,99,100,149).

During the 1930's and 1940's much of the literature focussed on the treatment of laryngotracheobronchitis. Initial writings focussed on the need for operative intervention using the bronchoscope to remove obstructing tissue and moisten the dried secretions. Jackson (37) suggested that antibacterial therapy in the form of hyperimmune serum could be beneficial.

The use of agents such as Belladonna and other sedatives for the treatment of laryngotracheobronchitis was specifically condemned by Jackson (37).

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With the introduction of antibiotics in the 1930's these were advocated and used for croup. Their use was associated with a drop in the mortality from laryngo-tracheobronchitis, although they did not always have the desired effect (80).

Kernan and Barach (150) were the first to suggest the inhalation of helium mixtures. They reported on 21 patients with obstructive lesions of the larynx and trachea, including 9 paediatric patients with evidence of laryngeal obstruction, who improved during the inhalation of a helium-oxygen gas mixture (60-80% helium). Subsequently a number of authors have reported beneficial results from the use of helium-oxygen mixtures in the management of croup (151-155) and other causes of upper airway obstruction (156-161). However a recent systematic review (162) concluded that there was insufficient evidence to support the use of helium-oxygen mixtures in the management of croup in children.

With the recognition of viruses as important aetiological agents for croup in the 1950's the emphasis moved away from antibiotic therapy to the use of humidification and other modes of therapy.

2.4.2 Humidification

From an early stage, the importance of adequate humidification of inspired air was recognised in patients in whom artificial airways had been introduced (22), and by extrapolation humidification of air was emphasized in the treatment of patients who had not been intubated or tracheostomized. This was picked up by Ingelstedt and Toremalm (163) who felt that there was a rational basis for the use of "vapour therapy" in croup. In a review of 893 cases of croup reported in Spain ambient humidification was provided to 95.5% of cases (interestingly 87.2% also received treatment with a water and alcohol impregnated neck collar (164).

Although humidification was felt to be essential for the management of patients with severe laryngotracheobronchitis, there is little evidence that it is useful for the treatment of the usual viral croup.

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In 1978 Lenney and Milner (141) studied 8 convalescent patients with croup who had residual inspiratory stridor to assess the response to phenylephrine nebulization. As a control 5 patients were given 2ml of sterile water by nebulization. They measured total respiratory resistance (R_T) using a forced oscillation technique before and after nebulization. No control patient showed any clinical improvement and the mean R_T at 5, 10, 15, 20 and 25 minutes after nebulization showed 7.5, 5.8, 7.6 and 7.2% increases respectively. One patient had a 24% increase in R_T! By contrast patients given phenylephrine showed a 30% mean reduction in R_T at 15 minutes.

Wolfsdorf and Swift (165) used an experimental model of laryngeal oedema in dogs and showed that airway obstruction decreased substantially when the larynx was exposed to warm or cold "dry" air, while humidified air (hot or cold) made no difference. Wolfsdorf et al (166) demonstrated that in nose breathing adults more than 80% of nebulized water is deposited in the nose, and with mouth breathing over 40% of nebulized water is deposited in the upper respiratory tract. They suggested that humidification of inhaled air would make minimal differences to the amount of humidification at the larynx.

Bourchier et al (167) performed a controlled study on 16 children (mean age 1.9 years) admitted to hospital with viral croup. Patients kept in a humidified atmosphere (temp 21-23^{o}C, relative humidity 87-95%) showed no benefit after 12 hours relative to control patients kept in normal room air. The study involved a small number of children, but large differences in response may have been noticeable.

Jamshidi et al (168) presented an abstract, but have not subsequently published a study in which a group of 46 patients (age 3 months to 6 years) with croup scores (using the modified Taussig Score) of 1 to 8 were randomized to receive humidified air or room air for 20 minutes. There was a significant improvement in croup scores (from 3.3 to 2.2) in the group receiving humidification while there was no change in the controls. Thirty six percent of humidified patients had a reduction in thoraco-abdominal phase angles, while none of the controls showed this, although 3 of the treatment group and 7 of the controls showed deterioration in phase angle.

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More recently Neto et al (169) studied 71 patients with moderately severe croup in the emergency department setting. Patients all received therapy with steroids (dexamethasone 0.6mg/kg orally) and were given nebulized adrenaline or budesonide at the discretion of the treating physician. The patients were randomized to receive either mist or no mist. There were no benefits or adverse effects attributable to the mist administration.

Scolnik et al (170) studied the effects of "standard humidification" (10 l/min of oxygen delivered through a 2m long by 2.2cm corrugated tubing with the addition of humidity from a high output nebulizer, directed at the patient's face from a distance of 20cm) – which was measured as providing the same humidification as ambient room air; vs 40% humidity and 40% oxygen delivered with a face-mask; and 100% humidification delivered as particle sizes with mass median diameter of 6.21μm again via a facemask. In a large randomized study in an emergency department, they showed no benefit from humidification when assessed using the Westley score 30 and 60 minutes after humidification.

Moore and Little (171) undertook a systematic review and meta-analysis of the data regarding humidification and croup. They were able to identify 3 randomized controlled trials (167-169) and concluded that they were unable to find evidence that the croup score of children managed in an emergency setting with mild to moderate croup improved substantially with inhalation of humidified air. Subsequently a review has questioned why clinicians continue to use humidification in croup when there is no evidence that it is useful (172).

Thus there is no reported evidence that humidification of inhaled gas is of benefit to hospitalized children with acute viral croup. Henry (173) reviewed some of the potential complications of mist therapy in small children including burns (if hot water is used as a source of humidification), overhydration and increased anxiety (particularly with the use of "oxygen tents").

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2.4.3 Steroids

Steroids as a mode of therapy were first introduced by Mårtensson et al (174,175). Rowe and Klassen (176) have reviewed some of the subsequent studies. Novik (177) was one of the first studies, followed by studies by Eden and Larkin (178) and Eden et al (179). Croup scores were not used in these studies, and the authors were not able to show differences in individual symptoms following the use of steroids. Skowron et al (180) used dexamethasone doses of 0.4 and 0.5mg/kg vs. placebo, and while stridor and the time to resolution of retractions seemed to be reduced, they felt that these benefits did not justify the risks of using steroids. The first steroid study using a croup score as an outcome measure was reported by James in 1969 (181), and this showed more rapid recovery on dexamethasone than on placebo. Leipzig et al (119) showed improved outcome (in terms of croup score) at 24 hours on dexamethasone (0.3mg/kg on admission and repeated 2 hours later) vs. oral saline.

In 1983 Koren et al (182) compared the efficacy of 0.6mg/kg of dexamethasone in the treatment of spasmodic croup and laryngotracheitis over a period of 6 hours using respiratory rate as the criterion of severity. They concluded after their study of 78 children that steroids offered some advantage to children with spasmodic croup, but none to children with laryngotracheitis.

Postma et al (183) reviewed the available literature on croup in 1984 and showed that it appeared that dexamethasone had a beneficial effect in doses of >0.3mg/kg.

Kuusela and Vesikari (121) performed a randomized double-blind, placebo-controlled study of dexamethasone and racemic epinephrine in the treatment of croup using a dose of 0.6mg/kg of dexamethasone. Of the 78 children studied 70 were described as fulfilling the criteria for "spasmodic croup". Outcome was assessed at 6, 12, 24 and 48 hours using a croup and cough score. They concluded that dexamethasone significantly improved the rate of recovery from spasmodic croup.

In 1989 Kairys et al (184) performed a meta-analysis of 10 reported randomized studies on steroids and croup involving 1286 patients. They did not differentiate

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between spasmodic and viral croup. The end-points used were clinical improvement 12 and 24 hours after treatment initiation and the rate of intubation. They concluded that there was improvement, attributable to steroids, in the condition of children hospitalized for croup. They also showed data suggesting that there was a dose-response effect which they postulated may partially explain some of the studies showing no effect.

Super et al (122) studied a group of 29 children with acute viral laryngotracheitis using a dose of 0.6mg/kg of dexamethasone given parenterally compared with saline placebo. They were able to show a significant improvement in the clinical score and the number of nebulizations required by the patients over a 12 to 24 hour period.

As David Smith put it in an associated editorial (185) "Corticosteroids in croup: A chink in the ivory tower?"

Dexamethasone given intramuscularly (0.6mg/kg) to outpatients with croup was associated with a reduction in severity of illness within 24 hours (124). Geelhoed and Macdonald (186) studied a group of children with mild to moderate croup and found that there was no difference in the outcome when patients were given 0.15mg/kg, 0.3mg/kg or 0.6mg/kg. However it is possible that the study was inadequately powered to assess equivalence (187)

A study of patients with mild croup (Westley grade up to 5 and mean approximately 3) showed no difference in clinical outcomes between treatment with 1mg/kg prednisolone, 0.15mg/kg and 0.6mg/kg of dexamethasone (188). There was no difference in reduction in clinical scores, but the authors acknowledged that the study was not sufficiently powered to exclude a difference in need for ongoing therapy later.

All the above studies used oral or parenteral steroids. The use of inhaled steroids in the form of nebulized budesonide for mild to moderate croup has been reported (133), concluding that nebulized budesonide was associated with an improvement in clinical score within 4 hours of treatment. A similar study in moderate to severe croup (127) showed clinical improvement within 2 hours of treatment with

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budesonide. In a further study Geelhoed and Macdonald (130) showed that, in children hospitalised for croup, there was no difference between inhaled budesonide (2mg dose) and dexamethasone syrup (0.6mg/kg) in terms of reduction in symptoms relative to patients given placebo. Johnson et al (189) found that in moderately severe croup, treatment with either nebulized budesonide (4mg single dose) or intramuscular dexamethasone (0.6mg/kg) was better than placebo (as assessed by rates of hospitalization and croup scores), while dexamethasone seemed to offer the most rapid clinical improvement.

The combination of inhaled budesonide (2mg) and dexamethasone (0.6mg/kg orally) was superior to dexamethasone alone in terms of improvement in croup score (small change) following therapy (190,191), in a outpatient population. A subsequent paper from the same group (190) however found no benefit from additional budesonide nebulization. Geelhoed et al also found no benefit from administration of budesonide following dexamethasone in a study in their emergency department observation area (192). In this study patients were given an oral dose of 0.15mg/kg of dexamethasone followed by 2mg of inhaled budesonide.

A review of patients transported to a regional paediatric intensive care unit in London with upper airway obstruction (193) noted that 35% of patients with croup were given nebulisation with budesonide, and these patients were significantly less likely to require intubation.

Luria et al (123) studied a group of children with mild croup (mean/median score on modified Westley score of 1.6 / 1) and compared the effects of oral (0.6mg/kg) dexamethasone with nebulized dexamethasone (160μg) and placebo. There were no differences between the groups at baseline, but the group receiving oral dexamethasone had fewer treatment failures (4% vs 16% and 14% in the nebulized and placebo group respectively), less need for additional therapy and reported greater clinical improvement on day 1 following treatment.

The issue of the effects of steroids on reintubation following intubation for severe croup has been addressed in a number of studies. Rajah et al (194) retrospectively reviewed 82 children who had been mechanically ventilated for croup. They

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concluded that steroid had no effect on the risks of reintubation. However their patients were intubated for a median of 9 days, and were only extubated in the presence of a positive leak test. Both the steroids and the doses given were very variable. By contrast Freezer et al (195) had previously reviewed 176 children who had been intubated for severe croup. They also extubated if a leak was present, but in addition children less than or greater than year of age were extubated on day 7 or day 5 respectively if a leak was not present. They showed that prednisolone administered at a dose of 2mg/kg/day for 36 hours commencing 24 hours prior to attempted extubation increased the success of subsequent extubation in patients who had failed the first extubation. Tibballs et al (196) randomly assigned 70 children who had been intubated for croup to oral prednisolone (1mg/kg down the nasogastric tube, 12 hourly) or placebo from the time of intubation until 24 hours after extubation. They found that prednisolone reduced the duration of intubation, the need for reintubation and the number of doses of nebulized adrenaline given after extubation.

A meta-analysis by Ausejo et al (197) considered the published data relating to the use of steroids in croup. They concluded that treatment with glucocorticoids appeared to be effective in improving symptoms within 6 hours. Approximately 5-7 patients needed to be treated in order for one to experience a significant improvement in symptoms. They did raise the concern that publication bias may have contributed towards this conclusion. It is however true that studies of the effect of steroid therapy on the rate of hospital or ICU admission and length of stay have shown a decrease subsequent to the introduction of steroid therapy to those regions (198,199).

Bjornson et al (187) undertook a randomized controlled study of 720 children with mild croup seen at 4 paediatric emergency departments in Canada. Patients were randomized to receive either placebo or dexamethasone (0.6mg/kg orally). The patients had mild croup (Westley score ≤2), and the group receiving dexamethasone had lower rates of return to medical care, more rapid resolution of symptoms, less disturbance of sleep and less parental stress. This article was reviewed by Custer (200) who highlighted the extent of the sleep disturbance and family impact of croup in childhood.

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Parker et al (201) addressed the question of the duration of stridor at rest in children with croup who had been treated with steroids. Following a dose of steroids the median duration of stridor at rest was 6.5 hours. Children with more severe croup had slightly longer duration of stridor.

The responses to steroids were reviewed by Landau and Geelhoed (202) who highlighted a possible link between a background of allergy and better steroid effects, as referred to by Martensson et al (175)

Table 2.6 summarizes the data from 32 studies on steroids in croup. Taken together the studies suggest that there is a clinical benefit in the use of steroid therapy in patients with mild, moderate and severe croup. However there were wide differences in patient groups (some groups are highlighted as being made up largely of patients with spasmodic croup, while others were made up of viral croup, with others where this information is not available). Croup scores were frequently used as the mode of assessment of croup severity, and relatively few studies focused on patient outcomes (rate of hospital admission, rate of intubation etc). The majority of studies focused on children with mild to moderate croup in the outpatient and emergency medicine setting. The data are heavily dominated by studies from a small group of centres (in Australia, the United States of America and Canada) with very limited data from developing countries.

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Table 2.6: Studies of steroids in croup

Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
Mårtensson et al, 1958 and 1960 (174,175)		Prednisolone (2.5mg if <1yrs and 5mg if ≥1yr) orally with subsequent repeated doses	
Novik, 1960	Hospitalized	Prednisolone	No difference in

Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
(177)	children	(2.5mg if <2yrs and 5mg if ≥2yr) orally with subsequent repeated doses	duration of hospitalization and stridor. Did note that 8 of children without steroids required tracheostomy within an hour of admission while none of the steroid therapy group required tracheostomy
Eden and Larkin, 1964 (178)	Patients admitted to hospital. No score provided but all had barking cough, inspiratory stridor and hoarseness	Methylprednisolone (1mg/kg) intramuscularly 6hrly for 24 hours vs control (not specified)	No difference between groups although both improved
Eden et al, 1967 (179)	Did not score severity of illness, but patients had stridor, dyspnoea retractions and some cyanosis	Dexamethasone (0.1mg/kg) intramuscularly every 6 hours	No apparent difference related to steroids
Skowron et al 1966 (180)		Dexamethasone (0.4 and 0.5mg/kg)	No statistically significant

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
		intramuscularly vs. placebo	differences
James 1969 (181)	Scored on dyspnoea (0-2) cyanosis (0-2) and sternal and subcostal retractions (0-3). No baseline data provided, but did exclude all patients with very mild stridor, persistent or congenital stridor and those with evidence of associated pneumonitis	Dexamethasone (4.5 to 8.6kg received 4mg, 9.1 to 13.2 received 8mg, and 13.6 or more received 12mg) given in a single intramuscular injection vs placebo	Clinical improvement in croup score on steroids
Ross 1969 (110)	Grading system which ranged from croupy cough to cyanosis (with grades of retractions in between)	Retrospective review of patients given treatment including corticosteroids	Improvement in clinical severity in those patients who were treated with " adequate" doses of corticosteroids (appeared to be single dose of 100mg of hydrocortisone)

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
Leipzig 1979 (119)	Croup score (Syracuse) with mean of 8.14 (placebo) and 8.46 (dexamethasone) out of maximum of 11	Dexamethasone (0.3mg/kg) as 2 doses 2 hours apart vs oral saline	Clinical improvement with croup score dropping to 1.19 at 24 hours in treated group vs. 5.58 in placebo group
Koren 1983 (182)	Respiratory rate was sole criterion	Dexamethasone (0.6mg/kg) intramuscularly vs saline	Improvement on spasmodic croup but no change in laryngotracheitis
Postma et al 1984 (183)	Whether patients required intubation	Average dose of steroids was dexamethasone 0.5mg/kg or "equivalent"	In a retrospective review no patient treated with steroids required intubation
Kuusela and Vesikari 1988 (121)	On a cough score 0-3 all started on 3, and on a dyspnoea score of 0-3 scores varied from 2.9 to 3.	Dexamethasone (0.6mg/kg) intramuscularly and racemic adrenaline vs Dexamethasone (0.6mg/kg) intramuscularly with placebo nebulization vs placebo intramuscularly with racemic	Dexamethasone improved rate of recovery from spasmodic croup

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
		adrenaline nebulization vs placebo injection and nebulization	
Super et al 1989 (122)	Mean Westley croup score 4.5	Oral dexamethasone (0.6mg/kg) vs. saline placebo	Significant improvement in croup score (from 4.5 to 1) and reduction in number of nebulizations
Husby et al 1993 (127)	Children admitted to hospital with moderate to severe croup. Croup score 8 (modification of Westley with maximum of 17)	Budesonide (2mg by nebulization) vs. saline	Improvement in croup score from 8 to 4.5 in budesonide group (no change in saline group) over 2 hours.
Klassen et al 1994 (133)	Patients in outpatient department. Median Westley croup score of 4	Budesonide (2mg by nebulization) vs. saline nebulization	Scores improved to 1 in the budesonide group vs. 3 in the control group
Cruz et al 1995 (124)	Outpatients with median of 2 (modified Westley) and range of 2-5	Intramuscular dexamethasone (0.6mg/kg) vs normal saline injection	Reduction in severity of illness within 24 hours

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
Geelhoed and Macdonald 1995 (186)	Outpatients with croup (croup score of 3.8 to 4 – using their own score with maximum of 6)	Oral therapy. Trial A: oral dexamethasone 0.6mg/kg vs 0.3mg/kg. Trial B: 0.3mg/kg vs 0.15mg/kg,	No difference in outcome. Scores improved in all groups and were not different between groups
Geelhoed and Macdonald 1995 (130)	Hospitalized children (scores of 3.8 –using their own score with maximum of 6)	Oral dexamethasone (0.6mg/kg) vs. budesonide (2mg by nebulization) vs. placebo	No differences between the steroid groups, but more treatment required for placebo
Geelhoed 1996, (204)	Outpatients with mild croup (croup score 0.9 using a specific score with maximum of 6)	Single oral dose of dexamethasone (0.15mg/kg) vs. placebo	8 of 50 in placebo group returned for further care vs. 0 in treatment group
Klassen et al 1996 ((190,191)	Emergency department of teriary hospital. Admission croup score of 3-8 after at least 15 minutes of mist therapy	All patients received oral dexamethasone (0.6mg/kg) and were randomized to either inhaled budesonide (2mg or 4ml) vs saline nebulization (4ml)	84% of the budesonide patients had a clinically significant improvement in croup score vs 56% for saline
Klassen et al 1998 (190)	Mean baseline croup scores	Oral dexamethasone,	Equal improvement in

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
	ranged from 3.5 to 3.8 on Westley score	(0.6 mg/kg), and nebulized placebo vs oral placebo and budesonide, (2 mg by nebulization); vs oral dexamethasone, (0.6 mg/kg), and budesonide (2 mg by nebulization)	all groups.
Johnson et al 1996 (205)	55 children seen in an outpatient department with a median croup score (Westley with minor modifications) of 4 (of 17 maximum)	Outpatient treatment with nebulized parenteral dexamethasone (10mg if <8kg, 15mg if 8 to 12 kg, 20mg if >12kg)	Significant improvement in croup score after 4 hours, but no difference in rate of hospitalization
Johnson et al 1998 (189)	Set of children in emergency department with mean croup scores of 3.8 to 4 (Westley score – max of 17)	Nebulized budesonide (2mg) vs intramuscular dexamethasone (0.6mg/kg)	Improvement in croup scores and reduced hospitalization in budesonide and dexamethasone, but dexamethasone associated with more rapid improvement

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
Rittichier and Ledwith 2000 (206)	Emergency department. Mean Westley croup scores 2.09 and 1.95 for the 2 groups respectively	Oral vs. intramuscular dexamethasone (0.6mg/kg to max of 8mg)	No difference between groups including need for subsequent interventions.
Luria et al 2001 (123)	Median / mean croup score 1 / 1.6 using a modified Westley score (max 18)	Oral dexamethasone (0.6mg/kg) with nebulized placebo vs nebulized dexamethasone (160µg) with oral placebo vs nebulized placebo and oral placebo	the group receiving oral dexamethasone had fewer treatment failures (4% vs 16% and 14% in the nebulized and placebo group respectively), less need for additional therapy and reported greater clinical improvement on day 1 following treatment
Donaldson et al 2003 (207)	Moderate to severe croup in an emergency department (baseline croup	Oral dexamethasone (0.6mg/kg) and direct pressure on thigh with needle	No difference between the groups on any parameters

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
	modified Westley score (max 18) 3.5)	hub vs. intramuscular dexamethasone (0.6mg/kg) with oral placebo	
Bjornson et al 2004 (187)	Patients in 4 emergency departments with Westley croup score of ≤2	Oral dexamethasone (0.6mg/kg) vs. placebo	Lower rates of return to medical care and more rapid resolution of symptoms, lower rates of sleep disturbance and parental stress
Amir et al 2006 (208)	Modified Westley score of 0-11, 3.6 and 2.4 in the 2 groups respectively.	Dexamethasone (0.6mg/kg) intramuscular vs betamethasone (0.4mg/kg) orally	Both groups improved with no difference between groups
Cetinkaya et al 2004 (209)	Average Westley croup scores of 2.5 to 3	Group 1 received budesonide (500µg by nebulization) plus a single dose of oral multivitamin syrup, and 2ml of intramuscular saline. Group 2 received 2ml of nebulized saline, plus a single dose of	All the steroid groups improved more rapidly than the placebo group. No differences between steroid groups at 24, 48 and 72 hours.

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
		oral multivitamin syrup, and a single dose of dexamethasone (0.6mg/kg to max of 8mg) intramuscular Group 3 received 2ml nebulized saline, plus a single dose of dexamethasone (0.6mg/kg to maximum 8mg) orally and 2ml of intramuscular saline. Group 4 received 2ml intramuscular saline, 2ml nebulized salbutamol solution plus saline and oral multivitamin syrup.	
Geelhoed 2005 (192).	Emergency department observation area. Baseline croup score 4.1 using their own score with maximum	All received dexamethasone (0.15 mg/kg) orally followed by budesonide(2mg by nebulization) or placebo	No additional benefit from budesonide

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Author	**Clinical severity at start of study**	**Medication and nature of study**	**Outcome**
	of 6		
Sparrow and Geelhoed 2006 (210)	Outpatients presenting with mild to moderate croup. Modified Taussig croup scores of 2 (max of 6)	Prednisolone (1mg/kg) orally vs. dexamethasone (0.15mg/kg) orally	No difference in croup scores and other clinical features, but the children given prednisolone were more likely to present again (29% vs. 7%)
Fifoot and Ting 2007 (188).	Westley croup score up to 5 and mean of 3	Prednisolone (1mg/kg), vs dexamethasone 0.15mg/kg and 0.6mg/kg (all orally)	No difference (not adequately powered to exclude a difference in need for ongoing therapy)
Chub-Uppakarn and Sangsupawanich 2007 (211)	Baseline Westley croup scores of 4.2 and 4.6 in 0.15 and 0.5mg/kg groups respectively	Dexamethasone 0.15mg/kg (max 3mg) or 0.6mg/kg (max 12mg) given intravenously	No difference between the 2 groups (relatively small study with only 41 patients in total study)

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Although there is broad agreement about the role of steroids and adrenaline in the management of croup, there are considerable differences in clinical practice in the details of this therapy. Borland et al (212) have reviewed clinical practice in 8 paediatric hospital and 3 mixed emergency departments in New Zealand and Australia. Although 9 of the 11 units had clinical practice guidelines for croup

management, there was considerable variation in the specific use of types, routes and dosages of both steroids and adrenaline. This issue has also been addressed by Hampers and Faries (213) in a study where they compared resource utilization by paediatric based physicians with those by emergency medicine trained physicians. The results showed that the emergency medicine based physicians used significantly more resources in the clinical management of children with croup. The groups had different utilization rates for parenteral and oral steroids.

Incorporation of steroid therapy (together with adrenaline nebulization) into clinical pathways has improved the outcome in a before and after study completed in Australia (214). Similarly McDonogh et al (215) reported that in Wales from 1986 to 1992 there was a substantial increase in the administration of steroids and nebulized adrenaline to patients with croup. Despite an increase in the number of patients admitted with acute viral croup, there was a marked reduction in the number of patients requiring either ICU admission or intubation.

None of the studies above reported deleterious effects from steroids. The use of steroids has however been associated with delays in diagnosis of airway haemangioma (216). Burton reported on candida laryngitis following use of steroids and antibiotics (217).

Cherry (13) recently made the comment that "..risks of steroid use have not been evaluated and, because of small sample sizes in all available studies, they cannot be evaluated by meta-analysis". He went on to describe 3 children with croup who developed complications on steroids, and referred to complications that may have been attributable to steroids in several studies (122,205,217). In a retrospective review of patients with croup who required airway intervention at the Red Cross War Memorial Children's Hospital, Hatherill et al (101) commented that the introduction of steroids had been associated with a sharp drop in the number of patients requiring intervention, but no increase in the proportion of patients with herpetic laryngitis (or candidal laryngitis). There are very few reports of complications of steroid therapy in croup despite the widespread use of steroids in this context over the last 1 to 2 decades. Although the data is incomplete, it would seem that there are potentially

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significant benefits to be obtained from the use of steroids in the management of croup with few if any serious side-effects.

2.4.4 Adrenaline nebulization

(216)The use of adrenaline for croup was first suggested by Davison (218) who reported that adrenaline (0.2ml aqueous solution of 1:1000) administered subcutaneously cleared obstructive symptoms of spasmodic croup within 15 minutes.

The use of racemic adrenaline for the treatment of post-intubation croup was first described by Jordan et al (219) in 1970. They recommended the use of 0.5ml of 2% racemic adrenaline given by nebulization with intermittent positive pressure ventilation (IPPB). The following year they published a 10 year experience (220) showing that use of this technique had eliminated the need for artificial airways among their patients. A similar experience was reported by Singer and Wilson (221) who had reduced the number of tracheostomies for croup to virtually zero by the use of racemic adrenaline given by IPPB.

Gardner et al (111) reported that 89% of children given racemic adrenaline by compressor and face-mask did show an improvement in clinical score after treatment. However the use of nebulized adrenaline did not reduce the overall duration of hospitalization or the incidence of tracheotomy in their patients with croup. This was confirmed by Taussig et al (115) who performed the first randomized, controlled study of nebulized racemic adrenaline given by IPPB to a group of patients with scores 6 to 12 (out of a maximum of 14). They demonstrated a significant clinical response to nebulized adrenaline within 10 minutes of the nebulization. This effect had disappeared by 2 hours and the natural history of the disease did not appear to have been changed. The results of Westley (116) showed a similar pattern with good initial clinical response to nebulized racemic adrenaline given by IPPB (when compared to nebulized saline given by IPPB).

In 1982, Fogel et al (117) reported that there was no apparent difference in effect when racemic adrenaline was administered by nebulization alone, or by nebulization

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with IPPB. They were treating a group of children with average croup scores (on a modification of the Westley score) of 5 – 7 (out of maximum 16) at the time of starting therapy. In keeping with the data of Westley and Gardner the clinical improvement attributed to adrenaline was not maintained beyond 1 hour.

Remington and Meakin (114) published a case report of a patient with acute severe croup who had responded to adrenaline (1:1000) given by nebulization. Racemic adrenaline is a mixture of the 2 optically active isomers of adrenaline (l- and d-adrenaline), while adrenaline solutions consist of the l-isomer. The l-isomer is 15 to 20 times more active than the d-isomer, and as pointed out by Ellis et al (222) there is no theoretical reason as to why the racemic preparation should be more effective or have fewer side effects. One potential problem of the adrenaline preparations commercially available is the fact that sodium metabisulfite is used as a preservative and this produces sulphur dioxide which may be irritant to the airways (223). Subsequently Waisman et al (126) showed that there was no difference in the effect of L-adrenaline and racemic adrenaline on the clinical course of patients with croup.

More recently Kristjánsson et al (128) showed a significant improvement in clinical score 30 minutes after administration of racemic adrenaline by nebulization. They focussed on a group of patients with mild to moderately severe croup and excluded patients with severe croup (score 10-15 on their specific score – see below). However there was no improvement in individual criteria including inspiratory stridor, retractions, air entry or oxygen saturation.

Although few serious side effects of adrenaline therapy have been reported, Butte et al (224) reported the case of an 11 year old boy who presented with clinical features of croup, and who developed transient ventricular tachycardia with subsequent radionuclide scan evidence of myocardial infarction following 3 doses of nebulized racemic adrenaline over a period of 55 minutes.

All of the studies described above have assessed the response to treatment on the basis of clinical assessment of croup. None of the clinical scoring systems of croup have ever been comprehensively validated against objective measures of the severity

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of the condition. In the following studies attempts were made to collect objective measures of the responses to treatment.

Oscillometry was used to assess the response of 8 infants in a convalescent phase of croup to nebulization with phenylephrine (141). Phenylephrine is a short acting α_1 agonist and would be expected to have a similar effect to adrenaline. This methodology revealed a significant but temporary drop in airways resistance (30%) of 7 of the 8 patients following administration of phenylephrine. It is not known whether phenylephrine has any effect during the acute phase of the croup.

Improvement following adrenaline nebulization was demonstrated in a flow volume loop on an 8 year old boy with croup (9).

Corkey et al (145) documented changes in radiographically assessed tracheal diameter in patients with croup following nebulisation (with intermittent positive pressure breathing) with either racemic adrenaline or distilled water. They showed that racemic adrenaline was significantly better at acutely relieving airway obstruction than distilled water.

Sivan et al (125) used measurement of thoraco-abdominal asynchrony (TAA) and some other measures of respiratory mechanics to assess the response of patients with upper airway obstruction (including 5 patients with croup and others with post-intubation stridor) to adrenaline nebulization. This study demonstrated a decrease in phase angle in patients following the administration of racemic adrenaline, together with an increase in tidal volume, mid-tidal inspiratory (MTIF) and expiratory flow (MTEF), and a decrease in the ratio MTEF/MTIF. Clinical improvement was also noted in 22 of the 29 patients.

Transcutaneous CO_2 pressure of patients with croup was shown to drop significantly following inhalation of nebulized racemic adrenaline by Fanconi et al (137). It is assumed from the data on pCO_2 that the effects of adrenaline nebulization are related to improvement in airway obstruction. There is animal data suggesting that nebulized adrenaline may increase respiratory drive (225). Although it is possible

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that adrenaline does not have any effect on the airway obstruction of croup (226), and that its effects may be related to stimulation of ventilation, it seems unlikely in view of the improvement in clinical scores that were seen simultaneously.

Weber (154) randomized children with moderately severe croup (mean modified Taussig score of 6.7 in the enrolled patients) to receive either nebulized racemic adrenaline, or continuous heliox administration. They showed a significant improvement in croup scores in both groups.

Thus although there are a number of studies suggesting that patients with croup may benefit from adrenaline nebulization, there are very few reported objective measurements of the effects of adrenaline nebulization on the mechanics of breathing in patients with croup.

2.4.5 Conclusions of treatment of croup

While humidification has not been shown to be efficacious, steroids have been shown to be effective in the management of croup in many studies.

There is good evidence that the administration of steroids improves symptoms within 6 hours of administration, and that in regions where steroids have been used for the treatment of croup the incidence of severe croup requiring endotracheal intubation has reduced. The development of scoring systems for croup was a critical feature in the research that led to the conclusion that steroids were efficacious. However the evidence base for the use of steroids would be stronger if the clinical definition and description of clinical groups was more standardized; if scoring systems had been objectively evaluated (this would affect the selection of patients for randomization as well as assessement of treatment response) and if the clinical endpoints for assessment of response (e.g. assessment of endpoints such as duration of hospital stay and need for further therapy may vary considerably from centre to centre) were more clearly delineated.

There is similarly good clinical evidence that symptoms in some patients improve after the administration of adrenaline to patients with severe croup. This effect is

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however short-lived, and there is no evidence that the use of adrenaline leads to a change in outcome. The effects of adrenaline have been assessed using clinical scoring systems, and also by a variety of objective methods including flow-volume loops and measurement of thoraco-abdominal asynchrony.

2.5 Conclusions

Croup is a common childhood condition which is well recognised and several modalities of treatment are in current use.

The nomenclature and literature of croup is confusing because of the different historical eras covered, and the different priorities of the authors. The pathogens have been well described, and there is some literature regarding the immunological responses in patients with croup. Although the pathology and pathogenesis of croup have been described, there is very little available literature regarding the mechanics of breathing in patients with severe croup. Further investigation of the mechanics of breathing in croup would improve understanding of this condition (and possibly other conditions associated with airway obstruction). Little is published about croup in developing countries (where different pathogens may be present, and where conditions such as malnutrition are more common).

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Clinical assessment of croup is confused by the variety of scoring systems available. Neither the clinical signs used in the scoring systems nor the systems themselves have ever been fully evaluated in terms of predictive power or in terms of physiological significance. While reasonable interobserver agreement has been demonstrated in research studies, the 2 studies of scores in situations that are more typical of the clinical context, have shown much poorer agreement. In the words of Newth (107) *"clinically one tries to predict the onset of respiratory failure ..... Such indications are all rather vague and some are very subjective"*. Despite the lack of validation of croup scores, much of the current therapy for croup is based on studies which relied on these scores for the assessment of responses to therapy. Development of objective measures of airway obstruction in croup would allow validation of some aspects of croup scores, and may provide helpful direction

towards clinical parameters which may be useful in assessment of severity of airway obstruction.

The therapy of croup remains controversial. The therapy of patients with croup would potentially be improved by the development of more validated croup scores (validation may include objective severity of airway obstruction; interobserver reliability; reliability in the prediction of the the need for specific interventions ranging from hospital admission to endotracheal intubation), and the definition of important clinical endpoints. Even specific patients may benefit from the availability of objective measures of severity of airways obstruction or validated clinical scores as not all patients respond identically to therapies and clearer assessment may reduce their exposure to unhelpful or potentially deleterious therapy.

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Chapter 3
Mechanics of Breathing: Introduction and Literature Review

"Mechanics is the branch of physics which considers the action of forces (or pressures) on moving or stationary bodies (i.e. the lungs or respiratory system). The dynamic mechanics of the respiratory system describes the behaviour of the lungs and chest wall during the breathing cycle." (227)

Mechanics of breathing is concerned with one basic question: how does air get into and out of the lungs? (228)

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3.1 Introduction

There are a wide variety of methods available for the measurement of the mechanics of breathing in infants and children (227,229). Essential elements of all breathing mechanics are the pressure changes generated within the chest and the flow of air which results from those pressure changes.

The measurement of flow and of pressure changes will be reviewed in this chapter with particular emphasis on the techniques applicable to the measurement of breathing mechanics in infants and small children with acute severe croup. It has been recognised for some time that large pressure swings were happening in the chest in severe croup and during 1960 Novik, in the discussion of an article by Leegaard (230), suggested that they would be discussing measuring of intra-tracheal or intra-thoracic pressure changes in croup. However there are only occasional reports of measurement of intrathoracic pressure change in croup.

3.2 Mechanics of breathing

During breathing the pressures required to move air are determined by the interaction between the resistance, inertance (the force required to initiate movement), and compliance of the different components of the system. Resistance is made up of the resistance of airways (from the alveoli through to the nasal orifices) to the flow of gas and also from the resistance of lung tissue to movement. Compliance is related to the compliance of the chest wall, the pleura, the lung parenchyma and the airways. For practical purposes inertance (particularly in the context of croup) can probably be ignored.

During active breathing, plethysmographic techniques can be used to measure alveolar pressure changes. The relationship between these pressure changes and air flow relate to the resistance of the airways (airways resistance or Raw). Likewise pleural pressure measurements will relate to the resistance of the airways and the lung (pulmonary resistance) and the compliance of the lung parenchyma and airways.

During mechanical ventilation or during relaxation of the respiratory muscles, airway pressure will relate to the compliance and resistance of the entire system (Respiratory resistance, Rrs).

Thus the exact components of respiratory mechanics which are assessed depend on the measurement systems used. These in turn will depend on the clinical constraints of the patients under investigation and the apparatus available to investigators.

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3.2.1 Acute severe croup

Patients with acute severe croup are critically ill with severely compromised airways. The majority of these children are less than 2 years of age and will not co-operate with any voluntary manoeuvres. In this setting of possible incipient respiratory failure, there are concerns that sedation may not be appropriate. Any methods used to study these patients must therefore comply with the following particular constraints:

a) must not interfere with the management of the patient including clinical assessment and treatment. As clinical assessment requires auscultation of stridor methods must not interfere with sounds audible at the mouth. Treatment may include urgent endotracheal intubation or nebulization with agents such as adrenaline, and methods must not limit access to the upper airway.

b) must cause minimal if any discomfort, and be tolerated by patients without requiring sedation over and above that which might be given as part of normal clinical management

c) must not require active patient co-operation

d) agents such as adrenaline are given as part of the management and methods must allow ongoing monitoring of cardiovascular parameters such as pulse rate and blood pressure.

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3.2.2 Sedation in Infant lung function studies

It is almost always necessary to use sedation to obtain reproducible lung function studies in infants, particularly if uncomfortable procedures such as passage of a naso-oesophageal tube or application of a facemask are involved. Chloral hydrate is one of the agents commonly used for sedation.

Although adverse effects of chloral hydrate in normal clinical usage have been reported including arrhythmias (231-233), and there are concerns about both the delayed clearance of the drug and potential carcinogenic side-effects, the drug has been extensively used for routine clinical sedation as well as sedation for lung function studies.

A study in puppies and normal infants (234) showed that chloral hydrate had no effect on CO_2 chemoreceptor responses, that CO_2 elimination and oxygen consumption appeared to be slightly increased in those given chloral hydrate, and

that the time spent in Rapid Eye Movement (REM) sleep appeared to be no different to normal in the group given chloral hydrate.

Studies in normal children showed no effect of chloral hydrate on lung volumes or flows (235,236) except for tidal volume which did decrease slightly (236).

Following an adverse event when a child with oropharyngeal obstruction was given chloral hydrate sedation, Hershenson et al (237) showed in rabbits that chloral hydrate selectively decreased activity in the genio-glossus muscle and could thus potentially exacerbate obstruction at that level.

Small changes, of no clinical significance, in respiratory rate in normal patients have been shown with the related drug triclofos sodium (238), while no change was demonstrated using chloral hydrate (235).

In bronchiolitic infants Mallol and Sly (239) demonstrated a drop in respiratory rate following the administration of 70-100mg/kg of chloral hydrate from 64.8 to 37.3 breaths per minute. This was associated with a significant drop in oxygen saturation.

In a study by Fanconi et al (137) patients with croup who were sedated demonstrated an improvement in croup clinical score and no deterioration as assessed by transcutaneous pCO_2 measurement and pulse oximetry.

In 1993 Steinberg (240) reviewed the case for banning the use of chloral hydrate. He discussed the literature relating the use of trichloroethylene and its metabolite (chloral hydrate) to the carcinogenesis in rodents and concluded that there was not adequate evidence to stop the use of chloral hydrate in humans, but that there should be changes in guidelines for use.

Thus at the time at which the data was collected from patients, it was considered unlikely that chloral hydrate in the dosage of approximately 50-75mg/kg would significantly affect the validity of results obtained from patients with croup, or would pose any risk to children affected. Subsequent to the data collection, further information has been published, much of which was summarized by Gaultier et al

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(241). They concluded that it was still reasonable to use chloral hydrate to sedate infants for lung function testing, on condition that: adequate monitoring was in place; resources were immediately available for resuscitation; care was taken with wheezy infants and the total dose of chloral hydrate did not exceed 120mg/kg. Subsequently there has been extensive literature regarding the safety of chloral hydrate, and it is likely that other agents should be used for procedural sedation for children (242) – not because of the serious adverse effects of chloral hydrate particularly (all sedative drugs have adverse effects), but because it may be relatively unpredictable in up to 20% of children, and may have prolonged sedative activity.

There is a potential risk to sedation of patients in incipient respiratory failure. However patients with acute severe croup at the Red Cross War Memorial Children's Hospital had been sedated routinely for many years without documented adverse events.

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3.3 Pleural Pressure Changes

The pressure applied to the system can be measured at a number of points. The driving pressure at the mouth can be measured (usually using flow occlusion techniques) and this represents the pressure across the total respiratory system. Alternatively alveolar pressures can be measured using plethysmography and this represents the driving pressure across the airways. Finally transpulmonary pressure can be measured, and this represents the driving pressure across the airways and the lungs. Transpulmonary pressures are measured from the pleural pressure changes during the breathing cycle.

The total pressure applied (Papp) to move air in and out of the lungs is made up of the pressure that must be exerted to overcome elastic forces (in the chest wall and lungs) (Pel), resistive forces (including resistance to airflow and resistance) (Pres) and inertial forces (Pin). As inertial forces are negligible during quiet breathing the equation of motion can be simplified to:

$$Papp = Pel + Pres$$

Further, since compliance is defined as volume divided by pressure and resistance as pressure divided by flow, the equation can be modified to:

Papp = Volume/Compliance + Resistance/Flow

In experimental animal models pleural pressures and pressure changes can be measured using intrapleural measuring devices. In normal human subjects this technique is too invasive and oesophageal pressure measuring devices are extensively used to measure pleural pressure changes.

The lower oesophagus is exposed to the pleural surface and if the oesophagus remains as a potential space with no communication with the mouth or the stomach, intra-oesophageal pressure changes should be nearly identical to pressure changes (ΔP) in the surrounding pleura (with some change relating to the elastance of the oesophageal wall). This assumes that there are no artefactual pressures from oesophageal pressure waves or conducted cardiac pressure waves. According to Baydur et al (243):

$\Delta Poes/\Delta Ppl = 1 + EesCeq$

where Ees is the oesophageal elastance and Ceq is the volume displacement of the measuring device, usually of the order of 0.002 ml. Senterre and Guebelle (244) measured the elastance (dPoes/dVoes) of the lower part of the oesophagus in 10 babies and found it to be 14.4 ± 3.4 cm H2O/ml so it is reasonable to use an approximation of 15cm H_2O/ml giving a result of $\Delta Ppl/\Delta Poes = \pm 1.02$ i.e. the oesophageal pressure change should slightly underestimate pleural pressure change. Occlusion studies have provided more data on this matter and will be discussed below.

Pleural pressure changes are also not homogeneously distributed throughout the chest as shown in animal studies (245-249) adult humans (250-252) and infants (253-255).

Farhi et al (246) showed that although the pressure swings within the pleural space were relatively uniform over most of the lung, in the apices and basal gutters of the dogs studied there were significantly different pressure swings.

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Daly and Bondurant (250) measured pleural pressure swings in seated normal men. The pleural pressure changes over different parts of the lung were different unless a significant pneumothorax had been created, and in general the ΔP was less in the upper chest than in the lower chest. When a pneumothorax had been induced, pressure changes at two pleural sites and in the oesophagus were identical.

Oesophageal pressures vary according to patient position and measuring device placement. Mead and Gaensler (251) showed that oesophageal pressure swings in adult human subjects were significantly higher in the supine position than in the erect posture. Irvin et al (252) studied oesophageal pressures during different patterns of respiration in normal adult volunteers. They demonstrated that different patterns of respiratory muscle activity resulted in different oesophageal pressure changes at different levels. More recently Mayock et al (253) demonstrated in an animal model that phrenic nerve stimulation may cause the oesophageal pressure swing to significantly underestimate the pleural and airways pressure swings.

In infants, Dinwiddie and Russell (256) studied the comparison of pleural and oesophageal pressures in 3 infants with pneumothoraces during the first three days of life. They showed that although absolute pressures within the oesophagus were higher than those within the pleural space, pressure changes within the chest were equivalent when measured by oesophageal or pleural catheters.

Thus it may be difficult to measure truly representative pleural pressure swings in normal patients, as there are differences depending on the position of the patient, the position of the oesophageal pressure probe and the methodology employed.

In adult patients the validity of oesophageal pressure measurements may be assessed by asking patients to perform static voluntary efforts with open glottis against a closed airway and measuring the transpulmonary pressure. This assumes that all areas of the lung are in communication with the mouth and that the compliance of the lung is such that pressures will be transmitted to the air within the lung. In infants it is not possible to validate measurements in this way. In 1978 Milner et al described the use of the "occlusion test" to validate oesophageal pressure measurement in neonates (257). In this technique intraoesophageal pressure changes

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are compared with pressure changes at the mouth after total occlusion of the airway. This is based on the assumption that with total occlusion of the airway no flow or volume change will take place, and pressure should then equilibrate throughout the respiratory system.

Baydur et al (243) reviewed the relationship between Poes and Pmouth during occlusions of the airway and showed that

$$\Delta Poes/\Delta Pm = [Cst,L + CA + Cuaw] / Cst,L$$

where Cst,L is the static compliance of the lung, CA is the compliance of the intrathoracic gas (0.001 l/cm H2O and Cuaw is the compliance of the upper airway (adult values from Jaeger during Mueller and Valsalva manoeuvres are respectively 0.002l/cm H2O and 0.007l/cm H2O). In expiration the equation becomes

$$\Delta Poes/\Delta Pm = [Cst,L - CA - Cuaw] / Cst,L$$

Thus the ΔPmouth should underestimate the oesophageal pressure changes (ΔPoes) marginally during inspiration and overestimate the oesophageal pressure changes during expiration. The extent of the difference will depend on the volume of the lung. At low or high pressures pleural pressures may not be evenly distributed and this would introduce further error.

Intraoesophageal pressure changes were found to underestimate airway pressure changes by approximately 20% by Milner et al (257). Beardsmore et al (258) pointed out that the dynamic characteristics of the 5 FG catheter used by Milner et al were inadequate and validated the use of a 6FG tube attached to a balloon for the measurement of oesophageal pressure. It was apparent however that the technique was only valid if painstaking care was taken to ensure that the balloon was appropriately inflated and positioned.

Asher et al (259) demonstrated that a water-filled 8 FG feeding catheter could be used to measure oesophageal pressure changes adequately in normal infants. The Poes/Pmouth ratios obtained with this technique were closer to those predicted theoretically than the results of Beardsmore et al (258) using an oesophageal balloon. These results were only reported for occlusions at FRC and with resting respiratory efforts. An advantage of this method was the relative ease with which the catheter could be placed and measurements taken. Disadvantages of water filled catheters are

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the fact that absolute intraoesophageal pressures cannot be measured and they are more prone to movement artefacts.

As studies moved from descriptions of respiratory function in normal neonates and infants to studies of patients with respiratory pathology further concerns regarding the validity of oesophageal pressure measurements were raised. Thomson et al (260) studied 15 intubated, very low birthweight infants and found that occlusion tests were unsatisfactory in 14 of the 15 infants. They did not specify the size of the balloon used, nor did they specify the exact position of the balloon in the oesophagus other than to say that it was placed in a position where Poes/Pmouth was closest to unity. They concluded that in sick intubated infants, oesophageal pressure cannot be reliably measured.

Beardsmore et al (254) studied oesophageal pressure changes in a group of 17 infants. In 10 of 11 infants it was possible to obtain satisfactory occlusion pressures, however in 8 of the 11 there was a progressive elevation of the ratio Poes/Pmouth when measured at lung volumes above the tidal range. They concluded that at high lung volumes or pressures oesophageal pressure changes may not be representative of pleural pressure changes.

LeSouef et al (261) studied the effect of chest wall distortion on oesophageal pressure swings in 12 preterm infants and found that chest wall distortion was associated with marked changes in the ratio of mouth to oesophageal pressure swings, concluding again that oesophageal pressure changes are an unreliable estimate of mean pleural pressure changes in preterm infants particularly in association with chest wall deformation during respiration. A possible problem with this study was that the infants were not intubated and therefore changes in upper airway tone related to REM sleep together with compliant upper airways may have contributed to the differences in occlusion pressures.

Heaf et al (262) performed further studies on the accuracy of oesophageal pressure changes in infants with a mean age of 60 days. Satisfactory Poes/Pmouth ratios could only be obtained in 5 of 15 sick infants. Several of the infants studied were on intermittent positive pressure ventilation and there was no comment as to whether

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this influenced the data. In addition only 2 of the sick patients were sedated for the study and it is possible that restlessness and movement by the patients could have interfered with the studies (as commented on by Coates et al, (263)). In all patients the Poes/Pmouth was less than 0.9, i.e. the oesophageal pressure changes were underestimated. The length of the oesophageal balloon used is not specified and it is possible that the balloon extended beyond the lower oesophagus either into the cardia of the stomach or into the upper oesophagus where Coates et al (263) suggest that the tracheal pressures may be transmitted to the oesophagus.

Coates et al (263) studied 8 intubated preterm infants with weights of 640-3700g and showed that it was possible to achieve Poes/Pmouth of almost 1. This was possible if the tip of the water-filled catheter was placed between the cardia and the carina, and the infant had to be at rest with no struggling over a period of several breaths. They concluded that even in the presence of chest wall deformation during respiration a water filled oesophageal catheter can be used to measure oesophageal pressure swings.

The discussion above has focussed on pressure changes in the pleural space (including the oesophagus). An underlying assumption for the use of body plethysmography for the measurement of thoracic gas volume is that pressure changes within the lung are relatively uniform. However the report by Godfrey et al (264) of the underestimate of thoracic gas volume in patients recovering from bronchiolitis suggests that this assumption may not be valid in the setting of lower airways disease in small children. As reviewed by Castile and Brown (265) this could be explained on the basis of pressure changes in non-communicating areas of the lung not being reflected by the mouth pressure, or alternatively by the possibility that over distended areas of the lung may become so stiff that pressure changes are not transmitted across them to the trapped gas.

It is possible that some of the difficulties with the measurement of pleural pressure swings discussed above may be the result of trapped intrathoracic gas, or areas of markedly diminished lung compliance. This may be compounded in premature infants in particular by the compliance of the chest wall.

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Thus measurement of intra-oesophageal pressure change using a water-filled catheter is an acceptable method of measuring intra-thoracic pressure change if the following conditions are met:

the response time of the manometry system is appropriate to the respiratory rate of the patient studied

the oesophageal catheter is appropriately positioned in the chest

there is not significant distortion of the chest wall as may be seen in small premature infants

equal distribution of intrathoracic pressure changes throughout the chest is not assumed in children with abnormal lungs.

3.3.1 Calculated values using pleural pressure changes

A number of parameters may be calculated from the pressure-time curve and can be used as measures of the effort expended during respiration.

3.3.1.1 Pressure time integral (PT_{int})

The pressure time integral is the parameter calculated by integration of the area under the pressure-time curve.

The use of integrals of pressure against time was first reported by McGregor and Becklake (266) who studied 5 adult normal volunteers, 5 patients with obstructive cardiac disease and 4 cardiac patients. They integrated the area under the pressure time curve to represent the mean oesophageal pressure and multiplied this by the calculated surface area of the lung at FRC. This parameter "force" was found to correlate well with oxygen consumption during breathing. As the calculated surface area of the lung at FRC would not change the integral of the oesophageal pressure change must have correlated well with oxygen consumption.

Robertson et al (267) found that a threefold increase in the area under the inspiratory Poes vs. time curve over 1 minute (PPTI) in anaesthetized dogs breathing against a variable inspiratory resistance was associated with an increase in oxygen

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consumption (VO_2) of 36ml/min. They also found that diaphragmatic blood flow increased exponentially with increasing PPTI.

Field et al (268) found that the integral of trans-diaphragmatic pressures over time correlated well ($r=0.74$, $P<0.001$) with the oxygen consumption of the respiratory muscles in adult human volunteers breathing against inspiratory resistance.

One theoretical justification for assessing the effort of breathing by the pressure time integral in obstructed breathing, is the fact that when airways are completely obstructed considerable effort may be expended in attempting to overcome the resistance, but if there is no air movement work of breathing (product of volume of gas moved and pressure change) will be zero (266).

3.3.1.2 Pressure rate product (PRP)

A less complex analysis of the relationship between pressure changes and respiratory rate can be obtained from the pressure rate product which is given by the product of the respiratory rate and the mean intrathoracic pressure change during each breath.

This has previously been reported by Klein and Reynolds (269) as the pressure time index. They did not validate the pressure time index, but found that it reflected clinical changes in effort of breathing in patients with severe upper airway obstruction. A benefit of this measure is the simplicity of calculation. It is not necessary to know points of zero flow, nor is it necessary to integrate areas; it can be calculated from a pressure trace which shows peak to peak change and respiratory rate.

3.4 Air Flow

Air flow can be measured can be measured using a variety of techniques (227). Flow is usually measured at the mouth using a pneumotachograph (or other devices) and this signal can be integrated to provide a volume signal.

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In measuring flow the two aspects which have be considered, are the extent to which the measuring system may interfere with the flow patterns of the patient, and the accuracy of the measurement system.

3.4.1 Measuring system

3.4.1.1 Measuring system effects

When air flow at the mouth is measured in non-intubated patients, the face has to be covered by some form of mask. The mask itself may cause alterations in air flow patterns. Fleming et al (270) demonstrated that application of a facemask rim to the face of sleeping term neonates resulted in significant decrease in respiratory rate and increase in tidal volume, but with no overall change in minute ventilation. Although Chernick and Avery (271) showed that application of a mask rim to premature infants caused an increase in end-tidal CO2 (suggesting underventilaton) this increase was small and may have been complicated by differences in level of sleep and arousal between the babies. Dolfin et al (272) also showed that application of a mask rim to the face of sleeping infants caused a 14.6% increase in tidal volume. This was felt to be due to stimulation of the trigeminal nerve.

Application of the facemask may also alter the position of the jaw, the head and the neck. As demonstrated by Carlo et al (273) flexion of the neck of infants caused a significant increase in the total pulmonary resistance. In preterm infants 15-30° deviation from the neutral neck position were shown to be insignificant while hyperflexion and in some cases hyperextension were shown to significantly affect airflow and pulmonary mechanics (274). Rotation of the neck has also been shown to alter the timing and pattern of tidal breathing in infants (275).

The deadspace of the pneumotachograph / facemask system may also have an effect on the respiratory pattern of the infant. This was demonstrated in the studies of Dolfin et al (272) where application of the pneumotachograph/facemask system caused an approximately 19% increase in minute ventilation which did not occur with application of the mask rim alone. In studies on 63 healthy newborn infants, Marsh et al (276) found that a deadspace of 26ml made a significant difference to

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respiratory rate, tidal volume, minute ventilation and work of breathing. The added deadspace made no difference to total pulmonary resistance. It has been recommended that the total deadspace of the pneumotachograph/facemask system should be < 1.5 – 2ml/kg (277)

Measurement of the deadspace of a mask may not be straightforward, as it may be difficult to estimate the volume of the mask which is taken up by the infant's face during application although it seems reasonably accurate to measure the volume of the mask (using water) and then subtract 50% (personal communication from group reported in (277)). It may also be possible to fill much of the mask with putty to reduce the deadspace. Again it may be difficult to estimate the effect of the deadspace of the mask, as streaming effects may mean that the entire volume of the mask does not play a role in the deadspace during breathing.

It is also possible that the facemask / pneumotachograph assembly could have significant resistance to airflow. The recommendations from the ERS/ATS Task Force on Standards for Infant Respiratory Function Testing (277) were that: "The combined resistance of the apparatus (including any valves, capnographs, etc.) should be <20% of the infant's intrinsic resistance at the mean flows likely to be encountered. Thus, as a rough guide …, the combined apparatus resistance should not exceed 1.2 kPa/L/s at 50 mL/s in spontaneously breathing preterm infants, 0.7kPa/L.sat100mL.s-1 in term neonates and 0.5kPa/L/s at 300 mL/s in infants and young children."

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3.4.1.2 Accuracy of flow measurement

Inspired and expired gases are different in terms of temperature, gas composition and humidity. All of these features may affect the accuracy of flow measurement (and therefore of all derived values). In 2000 Frey et al (278) reviewed the specifications for data processing in the assessment of infant lung functions. They recommended that corrections should be applied for gas conditions during breathing using the following formula:

$$V'BTPS = V'ATP \times 310.2 \times (Pamb - PH_2O) / (273.2 + t) \times (Pamb - 6.3)$$

where V'ATP is the flow at ambient temperature, t is the ambient temperature (C), Pamb is the ambient barometric pressure (kPa), and PH_2O is the water vapour pressure (kPa) of the ambient gas.

At the time at which the data was collected, equipment was not available to measure all these parameters, and so for purposes of this study, it was decided that flow data would not be corrected for pressure, temperature and humidity conditions. Some data was subjected to a trial of correction, and this did not make a significant difference to the results of the studies.

Pneumotachographs are also sensitive to gas viscosity (278), so if gases of different composition (e.g. varying oxygen concentration) are to be given to the patient correction factors may need to be applied. In this particular study all infants were on room air (although oxygen saturation was monitored throughout) during the measurements of lung function. Oxygen was given as part of the process of nebulization with adrenaline and saline.

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3.4.2 Calculated values using air flow measurements

There are a variety of values which can be calculated using data from measurements of flow over time.

3.4.2.1 Tidal Volume

Tidal volume is the volume of air moved in and out of the respiratory system during a single breath. This can be measured directly using volume based devices, or may be calculated from flow and time data by integration.

There are differences reported between tidal volumes recorded using volumetric devices and those calculated by integration of the flow signal.

A potential problem in the calculation of tidal volume is the fact that inspired and expired gases are different in terms of temperature, humidity (or water content) and to a lesser extent gas composition. These can be corrected for using assumptions

about the characteristics of the gases, or using linear regression systems to account for the "drift" that will occur as a result of the gas characteristics.

Tidal volume is often used as the basis of averaging data from several breaths. It is possible to average data on the basis of time (i.e. time during the breath) or on the basis of proportions of tidal volume.

In order to compare data between patients of different size tidal volume may be corrected for body weight or length.

3.4.2.2 Minute ventilation

Minute ventilation is the amount of air that is breathed in or out during the course of 1 minute. This is derived from the tidal volume and respiratory rate and may also be corrected for body size.

3.4.2.3 Tidal flow volume loop analysis

The prospect of being able to assess airway obstruction from the analysis of tidal flow volume loops is attractive for a number of reasons. This methodology would not require patient co-operation, would be non-invasive and could potentially be used on sleeping children without having to use sedation.

A number of variations on the use of the forced expiratory flow volume loop have been described. Wise et al (279) described the use of crying flow volume loops in neonates, while Beardsmore et al (280) assessed the use of cough flow-volume relationships in normal and asthmatic children of school-going age. Both of these techniques did not require much patient co-operation, but did not look at tidal breathing patterns.

Morris and Lane (281) reported the use of the tidal flow volume loop to assess airways obstruction in 3 groups of adult patients. The groups consisted of normal volunteers, a group of patients with airflow obstruction (some asthma and chronic airway obstruction in others) and a group of patients with restrictive lung disease.

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Patterns of flow varied between the groups. The parameters percent expired volume expired at peak expiratory flow rate (Vpef/Ve%) and percent expiratory time at peak expiratory flow rate (Tmef / Te_{TOT} %) differentiated patients with obstructive lung disease from the others quite clearly. There was less variability in the expiratory flow pattern in obstructed patients than in others. There was good correlation between the FEV_1, FEV_1/FVC and SGaw and the Vpef/Ve % and Tmef / Te_{TOT} %. Further studies were recommended to consider the use of the parameters to measure differences in severity between different patients with the same conditions.

Abramson et al (282) reported on the use of tidal flow volume loops to identify different groups of intra- and extra-thoracic airway obstruction. The study population consisted of 100 preterm and term newborns and infant with an age range of 3 hours to 18 months. Thirty-five of the patients were clinically normal, while 65 had evidence of laryngotracheal or peripheral airways disease. The major feature described in this paper is the flattening or plateau of the inspiratory or expiratory flow volume loops depending on the site of the obstruction. They did no numerical analysis of the flow volume loops, other than to comment that the ratio of the mid-tidal inspiratory and expiratory flow rates was not helpful (this is a parameter used in forced inspiratory and expiratory flow volume loop analysis).

Martinez et al (283,284)(284), used the Tmef / Te_{TOT} ratio in infants and young children and found that a low Tmef / Te_{TOT} was associated with subsequent lower respiratory tract disease. They found that low Tmef / Te_{TOT} correlated with decreased airway conductance and hence with increased airway resistance.

Cutrera et al (285) assessed the use of Vpef/Ve % in normal patients and in asthmatics undergoing histamine challenge tests. They found that there was an intrasubject variation coefficient for Vpef/Ve % of 21.8% ± 0.7%. While Vpef/Ve % was not able to differentiate between asymptomatic asthmatic and normal subjects, there was good correlation between changes in Vpef/Ve % and changes in FVC, FEV_1 and other lung function parameters following histamine challenge. Despite the wide variability of the test, they concluded that the Vpef/Ve % ratio is a "simple and practical indicator of bronchial obstruction in infants, in school-age children, and in adults...".

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Tidal flow-volume loop analysis has also been used (274) to assess optimal treatment of infants with tracheobronchial abnormalities.

Aston et al (286) used the tidal breathing indices in infants during histamine challenge tests and compared these with data obtained used forced expiratory manoeuvres. They concluded that the Tmef / Te_{TOT} during expiration was an insensitive measure in infants and cannot be used to assess the histamine bronchial challenge. In their study there was actually an increase in the mean tidal expiratory flow despite a fall in maximum flow at FRC suggesting that these infants had adopted a strategy of active expiration in response to histamine.

Similarly Clarke et al (287) found that the Tmef / Te_{TOT} tidal expiratory flow index was an insensitive measure of airway function in infants when compared with maximum flow at FRC using a squeeze technique.

Mikkilineni and England (288) reviewed some of the factors which may affect the Tmef / Te_{TOT}. Aside from airways resistance other factors such as level of sleep, raised pCO_2 and the level of activity of muscle groups outside the airways could all affect Tmef / Te_{TOT}. They concluded with the comment that "... On the other hand, changes in Tmef / Te_{TOT} could be useful as a non-invasive measurement to follow individual children with severe lung disease and to evaluate their response to therapy."

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More recent studies (289-291) have shown that there is a correlation between Tmef / Te_{TOT} and lower airways obstruction albeit a weak one.

The use of the Tmef / Te_{TOT} remains controversial (292). Recent results suggest that the parameter may have limited usefulness despite the attractiveness of the technique. The parameter has never been assessed in patients with acute severe croup.

Other parameters which could be assessed from the tidal flow volume loop such as the area within the loop (as has been suggested in analysis of the maximal expiratory flow volume loop (293) have not been assessed in children and may be useful.

3.5 Relationship between air flow and pleural pressure changes

The relationship between pleural pressure changes and air flow can be examined in a variety of ways. Firstly it can be considered graphically where phase shifts; flow limitation and particularly shape of curves can be considered. Alternatively it can be considered by deriving values from formulae involving both pressure changes and flow changes e.g. resistance. Finally it can be assessed by looking at the relationship between values derived from pressure and flow data e.g. work of breathing or "efficacy" of breathing.

3.5.1 Graphic representation

Graphic representation is important as it allows an interpretation of the interrelationship between flow and pressure over the course of breaths, based either on the time of the breathing cycle, or on the volume of air moved during the breath.

Points at which relationships change markedly are of particular interest. An example of this is flow limitation where the air flow in response to pressure changes ceases to change.

3.5.2 Calculated data using both pleural pressure changes and air flow related data

The relationship between pressure changes and subsequent air flow depend on the resistance and compliance of all the components of the respiratory system.

When pleural pressure changes are measured the compliance and resistance of the pleura, the lungs and the airways are related to the subsequent air flows.

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The resistance of the airways is expressed as the driving pressure divided by the air flow obtained (usually cm H_2O/L/s). The reciprocal of this is the conductance of the airway (L/s/cm H_2O). As the lung volume changes, so the size and shape of the intrathoracic airways changes, and so conductance is often corrected for the lung volume at that particular point in time and becomes the specific conductance (Sgaw)

Initially these parameters were calculated for the breath as a whole, or for the duration of inspiration and expiration. Modern computer technology however now allows calculation of these parameters at multiple points throughout the breath.

3.5.2.1 Resistance

Resistance can be calculated in a number of ways from flow and oesophageal pressure data. The resistance will represent pulmonary resistance or the resistance across the space from the pleura to the mouth. The two methods used most frequently are those of Mead and Whittenberger (294) and Bhutani et al (295).

In the Mead and Whittenberger technique (294) pressure change required to overcome the elastic recoil of the lung is estimated from the points of zero flow and assumed to vary in a linear fashion (with volume) between these 2 points. If in fact the elastic recoil does not increase in a linear fashion with inspiration (e.g. becomes progressively steeper as the lung over distends) then the calculated resistance will be less than actual during inspiration.

In the technique of Bhutani et al (295) a least mean square analysis is used with the formula:

$$P = V/C + R.flow,$$

where P = driving pressure, V = volume, C = Compliance and R = resistance, assuming that the gas acceleration constant is negligible.

3.5.2.2 Work of breathing

The work of breathing can be calculated from the product of pressures developed and the volume of air displaced during breathing (296).

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Over a breath this can be calculated by integration of the area within the pressure volume curve. As work is also done by the elastic recoil of the respiratory system, the area between the oesophageal pressure at end-expiration and the expiratory volume curve can also be included in the calculation.

When comparing data between patients of different size, work calculated in this way should be corrected for body size, either using body weight or height.

The work of breathing does however not take the respiratory rate into account, and the rate of work of breathing can be calculated by multiplying the work of breathing by the respiratory rate. This has been referred to as the rate of work of breathing or the minute work of breathing.

The rate of work of breathing has been studied in infants (1.5 to 24 months) with bronchiolitis and bronchopneumonia (297), where it was found to be approximately 3 times the normal (range 2-6 times that in normal infants). The mean work of breathing per litre of ventilation was found to be twice the normal mean. Another study of work of breathing in infants with bronchiolitis (298) showed a six fold increase in the minute work of breathing. They suggested that the fact that sedation was not provided in their study explained why results were so much higher than those of Krieger and Whitten.

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3.5.2.3 Efficiency of breathing

Respiratory muscle efficiency is the ratio of the work of breathing to the oxygen consumption of the respiratory muscles (299,300). This parameter has however been found to have a wide variation (268) which may relate to methods of measurement of oxygen consumption, work of breathing as well as factors such as variations in chest wall dynamics and movement coupling during breathing.

An alternative approach would be to consider ventilation achieved (minute ventilation) and the effort of breathing (as represented by the pressure time integral), and this term could be called “volume for effort”.

3.6 Conclusions

The literature reviewed showed that a potential system for measuring oesophageal pressure changes during tidal breathing had the possibility of providing a reasonably accurate means of establishin pleural pressure changes and then deriving a number of parameters from these measurements. There is minimal published literature regarding the pleural pressure changes in patients with croup. This information is fundamental to an understanding of airway resistance and the effort of breathing in patients with croup.

Addition of a method for measuring air flow (using a facemask) would potentially provide a means of measuring and documenting the mechanics of breathing in patients with acute severe croup. This system would: not interfere with clinical management of these patients; impose extra invasive procedures; would be reproducible in other centres using equipment that would be relatively readily available in most intensive care units.

This study therefore set out to evaluate a group of patients (and normal controls) with acute severe croup, using a water-filled oesophageal catheter for measurement of intrathoracic pressure changes, and a facemask with pneumotachograph for measurement of air flows and volumes. We chose to calculate a wide variety of parameters from the available data, so as to evaluate a range of measures of respiratory mechanics in these patients. As part of their normal treatment, these patients were receiving adrenaline nebulization, and so we measured respiratory mechanics before and after nebulization with either saline or adrenaline. In addition to the objective measurements, we collected the clinical data required for an evaluation of the Klein score throughout the studies.

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Chapter 4
Patients and Methods

4.1 Introduction

This chapter provides an overview of all the patients studied in this set of observations, and a description of the methodology used for measurement of the mechanics of breathing.

At the time of data collection, patients with acute severe croup at the Red Cross War Memorial Children's Hospital were routinely sedated with 50-100mg/kg of chloral hydrate if agitated, and once sedated 8FG soft nasogastric tubes were passed and used to ensure adequate nutritional intake. This clinical protocol had been in use for many years and had not been associated with significant complications (personal communication, M Klein).

Validation of the methodology was undertaken by:

Collection of data from normal control patients

Analysis of reproducibility of data from patients with croup and controls.

The study was approved by the Ethics and Research Committee of the University of Cape Town (Ethics and Research Committee Protocol number 007/88). In all cases studied, consent was obtained from a parent who remained with the child throughout the collection of data.

4.2 Patients

4.2.1 Patients with croup

Twenty-one patients (table 4.1) were admitted to the study (convenience sample). They were all admitted to the Red Cross War Memorial Children's Hospital with clinical features of acute viral croup at a time when the researcher and a pulmonary

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technologist were available. Patients with other causes of laryngeal obstruction including measles, haemangiomata, subglottic stenosis and laryngeal papillomata were excluded. Satisfactory oesophageal pressure traces were obtained on 20, a trace was originally collected on patient 4, but this was subsequently excluded in view of technical difficulties.

All patients had severe croup at the time of entry into the study with 2 assessed as grade 2 (Klein score) and the rest as grade 3. All had received epinephrine inhalations previously, the last dose being at least 30 min prior to the study. None had received steroid therapy as these data were collected prior to the routine usage of steroids in croup. No infant had a previous history of endotracheal intubation or laryngeal obstruction.

4.2.1.1 Baseline croup studies

Single acceptable flow and pressure traces which could be processed and interpreted were obtained on 20 children with severe croup (see details in table 4.1a). The median age and weight were 11.7 months (range 3.6-23.7 months) and 9.3 kg (range 5.76-14 kg) respectively.

Three acceptable traces at 5 minute intervals with no intervening intervention such as adrenaline nebulization were available on 10 patients (3 female and 7 male) aged 3 to 23 months (median 8.7 months) and weighing 7.9 to 12 kg (median 8.93 kg). These studies were used to assess the trace to trace variability of the methods and for statistical analysis.

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Table 4.1a: Patients with croup – individual data

Patient	Sex	Age (m)	Weight (kg) (centile)	Length (cm) (centile)	Weight for height centile
1	Male	13.3	9.2 (10.9)	69.5 (0.17)	83.0
2	Male	9.8	10 (69.2)	76 (83.9)	47.8
3	Male	14.0	9.6 (20.0)	76 (16.1)	29.2
4	Male	6.7	7.9 (38.0)	65 (6.7)	84.7
5	Female	11.7	5.76 (0.02)	63 (0.01)	17.6
6	Female	6.5	7.94 (69.5)	66.5 (45.9)	76.5
7	Male	11.7	11.5 (90.3)	77 (68.2)	90.6
8	Male	12.4	11.5 (86.7)	73 (9.5)	99.3
9	Male	13.5	9.14 (9.2)	74 (8.5)	29.0
10	Male	3.6	6.52 (54.8)	61 (26.1)	79.1
11	Male	23.7	14 (87.2)	89 (68.3)	87.8
12	Female	6.2	6.56 (19.6)	62 (5.3)	74.1
13	Male	15.3	8.76 (2.4)	76 (9.6)	5.7
14	Male	6	8.82 (84.2)	66 (24.9)	96.4
15	Male	8.7	8.3 (21.4)	67.7 (5.5)	69.1
16	Male	7.5	9.46 (81.3)	62 (0.1)	99.8
17	Male	9.8	9.5 (51.1)	74 (59.3)	46.1
18	Male	13.1	12 (91.6)	79.3 (76.1)	90.0
19	Male	16.5	11 (43.8)	87 (98.0)	7.8
20	Female	8.6	9.1 (76.1)	69.5 (44.1)	86.9
21	Male	14.3	11 (59.5)	7.5 (33.8)	74.5

Patient 4 was subsequently excluded as a result of technical problems with the oesophageal pressure trace.

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Table 4.1b: Patients with croup, studies performed

Patient	Croup Score (Klein)	Repeated Baseline trace data available	Subsequently intubated	Adrenaline nebulization data	Adrenaline and saline nebulisation data
1	3	Y	Y	Y	
2	3	Y	Y*	Y	
3	3	Y		Y	Y
4	3				
5	3		Y		
6	3	Y		Y	Y
7	3		Y	Y	
8	2	Y	Y*	Y	Y
9	3	Y		Y	
10	3	Y		Y	
11	3		Y*		
12	3	Y	Y	Y	
13	3	Y		Y	Y
14	3	Y	Y	Y	
15	2				
16	3	Y		Y	
17	3			Y	
18	3	Y		Y	Y
19	3		Y*	Y	
20	3	Y		Y	
21	3		Y	Y	Y

* Studied before and after intubation.

Patient 4 was subsequently excluded as a result of technical problems with the oesophageal pressure trace.

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4.2.1.2 Patients with croup who were subsequently intubated

Nine patients were subsequently intubated for severe airways obstruction (see table 4.1b) and in 4 (weight 10 to 14 kg, median 11.3) (patients: 2, 8, 11, 19), intubated with Ivory Portex endotracheal tubes (3.0-mm internal diameter uncuffed endotracheal tubes, resistance 9 cm H_20/L/s at 0.2 L/s; Portex, Hythe, UK), studies were performed before and after intubation.

4.2.1.3 Patients with croup following adrenaline nebulisation

Studies were performed on 17 patients (tables 4.1a and b) following adrenaline nebulisation (see details below). The median age and weight were 12.4 months (range 3.6–23.7 months) and 9.2 kg (range 6.5–14 kg), respectively. All were severely affected: two cases with Grade 2 and the remainder with Grade 3 obstruction as assessed by the Klein score.

It was possible to perform studies before and after both saline and epinephrine nebulization on six patients aged 6.5–15.2 months (median 13.5 months) and weighing 7.9–12 kg (median 10.3 kg).

Adrenaline in normal saline or normal saline alone were both given by nebulization. Either 2 ml of 1:1000 or 1mg/ml (i.e. 2 mg) adrenaline with 2 ml of 0.9% saline, or 4ml of 0.9% saline were put into a Hudson nebulizer (Hudson RCI, Temecula,CA, USA). In each case the mixture was nebulized using oxygen with a gas flow of at least 6 L/min for a period of 5 minutes.

Physiologic measurements and collection of Klein croup score data were made immediately before and immediately after nebulisation, where possible ongoing measurements and data collection were continued at 5 minute intervals.

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4.2.2 Normal controls

Five children (3 male and 2 female) with no respiratory symptoms, who had been sedated (50-75mg/kg of chloral hydrate) for EEG studies as part of routine investigation of generalized seizures were studied as normal controls (Table 4.1). These patients were studied after the EEG study had been completed, they were not given extra sedation and a number of patients did not complete the study because they awoke on attempted passage of the nasal catheter.

None of these patients had a history of previous respiratory disease other than upper respiratory infections. No patient had been intubated at birth or for any surgical procedure. There was at least a month's interval between a previous respiratory infection and the study. One patient was excluded because of a history of intermittent snoring.

All these patients were below the 50th centile for height and weight, and one patient was below the 3rd centile for height and weight although the mean centile for weight for height was 43.74. There was no significant difference in age, weight or length between these patients and the patients with croup.

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Table 4.2: Control Patients

Patient	**Sex**	**Age (months)**	**Weight (kg) (Centile)**	**Length (cm) (Centile)**	**Weight for Height (Centile)**
1	Male	5	6.58(23.43)	64(23.91)	36.65
2	Male	11	11.5(3.78)	82(13.04)	57.03
3	Male	13	9.94(7.37)	75.5(18.65)	50.4
4	Female	14	9.3(19.82)	74(26.37)	46.66
5	Female	31	9.98(0.05)	79(0.73)	27.98
Median (range)		**13 (5-31)**	**9.94 (6.58-11.5)**	**75.5 (64-79)**	

4.3 Sedation and monitoring

Patients and control subjects were sedated with oral chloral hydrate (50-100 mg/kg) and studied while lying on their side using the technique of Asher et al (259). Oxygen saturation and pulse rate were monitored continuously by pulse oximeter (Nellcor Inc., Hayward, CA, USA). None were receiving oxygen on admission to the study, nor did any require oxygen during the studies. Oxygen was used as a driving gas for nebulisation (see below). Resuscitation facilities and a paediatric intensivist were immediately available at all times during the study.

4.4 Oesophageal manometry

Oesophageal pressure change with tidal breathing (ΔPoes) was measured with a pressure transducer (1290A, Hewlett-Packard, Waltham, MA, USA) coupled to a water-filled 8 French (1.0 mm internal diameter) vinyl plastic feeding tube. The tube was passed transnasally, after topical anaesthesia (2% aqueous lidocaine drops), to lie in the distal oesophagus by first passing it into the stomach, withdrawing it until a negative inspiratory pressure trace was obtained, and then a further 1 cm before fixing it to the face with tape.

Prior to each study the pressure transducer was calibrated against a water manometer. After passage into the stomach the tube was flushed with sterile water to clear all bubbles and debris, and then connected to the pressure transducer. The catheter was flushed regularly with sterile water. The response of the apparatus was linear to 9 Hz in the range 0 – 100 cm H_2O.

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4.5 Flow measurement

Flow was measured with a differential pressure transducer (Sanborn 270, Hewlett-Packard, Waltham, MA, USA) and heated pneumotachograph (Fleisch 0, resistance 5 cm H_2O/L/s at 0.2 L/s) coupled to a facemask (Vital Signs, #2, Totawa, NJ, USA) or directly to the endotracheal tube of intubated patients. The response of the pneumotachograph and transducer was linear in the range 0 - 0.2 L/s and 1-10 Hz. The phase lag between the flow and pressure manometer systems was less than 10 ms. Prior to each study the pneumotachograph was calibrated against flow as measured using a rotameter.

The face mask was applied gently for short periods of flow data collection with the head in slight extension but with no rotation (275), using therapeutic putty (Carter's, Westbury, Wiltshire, UK) to seal leaks. Data were collected after stabilization of pressure changes related to face mask application.

4.6 Processing and analysis of data

Flow signals, oesophageal pressures (Poes) and peak-to-trough changes (ΔPoes) were recorded with a polygraph (775B Hewlett-Packard, Palo Alto, CA, USA) on heat sensitive paper at 25 or 50 mm/s.

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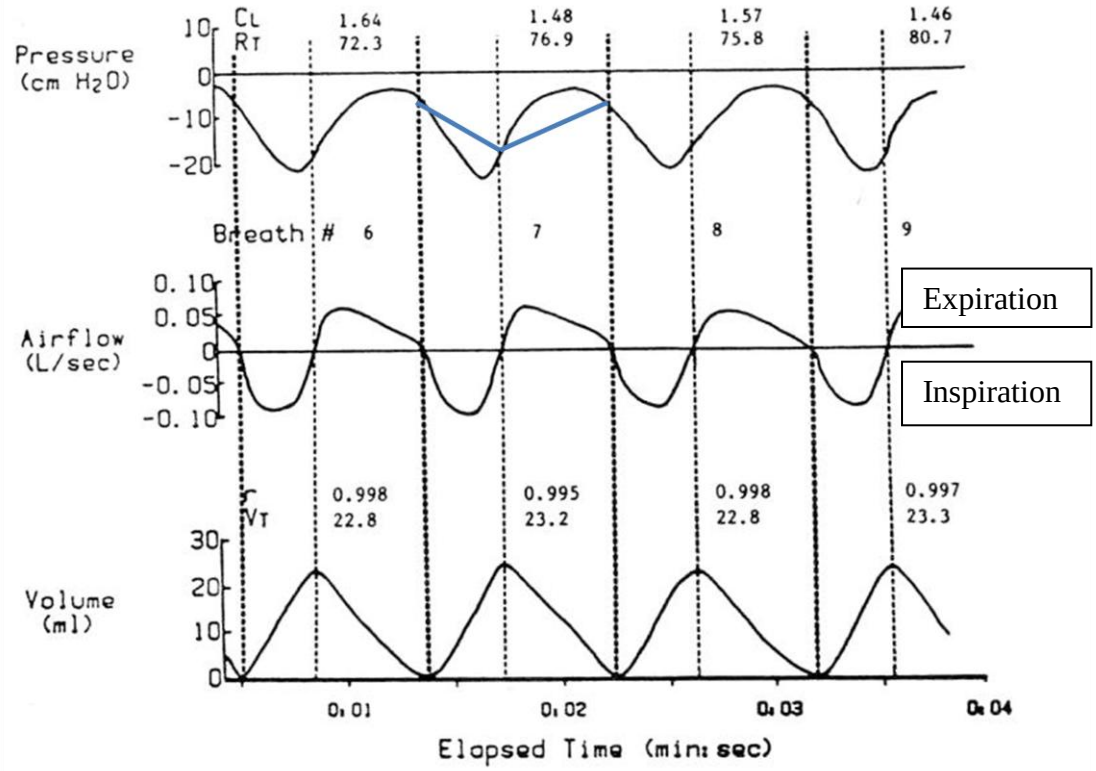
4.6.1 Data Analysis

The analysis was based on that of Mead and Whittenberger (294) by which the physical properties of the lungs in spontaneously breathing subjects were determined electronically, utilizing variations in oesophageal pressure as a measure of variation in intrapleural pressure (294). In this technique pressure change between points of zero flow was assumed to be related to compliance, and was assumed to vary in a linear fashion over the range of tidal breathing. We assumed atmospheric pressure at the airway opening (mouth).

Representative samples of three to ten breath sequences showing minimal breath-to-breath variation in pressure and flow were selected by inspection and entered into a personal computer by manually tracing the graphs on a digitizer board (Summasketch Plus, Summagraphics, Fairfield, CT, USA), and analyzed using custom-written computer programs (see appendix for details). Sample-to-sample variation in flow and ΔPoes were < 6 percent with breath-to-breath variation less than 10 percent.

Figure 4.1: Calculation of resistance



In this figure (modified from Bhutani et al, (295)), the blue lines represent the oesophgaeal pressure change between points of zero flow (thus due to compliance) and the gap between those lines and the oesophageal trace represent pressure required to overcome resistance.

Respiratory rate and inspiration to expiration ratios (I:E) were derived from the mean respiratory cycle time and respective phase intervals on the flow trace. Volume was derived by integration of flow with respect to time. Tidal flow-volume analysis included time to peak inspiratory flow as a proportion of inspiratory time (Tmif / Ti_{TOT} (%)), time to peak expiratory flow as a proportion of expiratory time (Tmef / Te_{TOT} (%)), the ratio of mid-expiratory and mid-inspiratory flow, and the area within the flow-volume curve (AFV (ml/s.ml/kg)). Lung compliance (C_L) was expressed as the volume change for the pressure drop between points of zero flow (294). Mid-tidal airway resistance ($R_{AW}0.5$) was calculated as the pressure drop per unit change in flow, after subtracting the pressure due to elastic forces (lung compliance, C_L) – see Figure 4.1 -(294) and was derived for inspiration ($R_{AW}0.5_{\mathbf{I}}$) and expiration

($R_{AW}0.5_{E}$) at 50 percent of the respective tidal volumes. Resistive Work of Breathing (WOB) was calculated as the area within the pressure-volume curve (296) The Rate of Work of Breathing was calculated from the product of the work of breathing and the respiratory rate. Breathing efforts were quantified to obtain surrogate measures of energy expenditure (301) by computing the area within the pressure-time curve (Pressure-Time Integral, PTint) and the product of the respiratory rate and the mean peak-to-trough ΔPoes (Pressure-Rate Product, PRP). Previously, the PRP has been referred to as the Pressure-Time Index (269).

We calculated the ratio of minute ventilation to PTint (Volume for Effort, VFE) as an index of the efficiency of energy expenditure on breathing.

4.7 Statistical analysis

4.7.1 Reproducibility

In order to assess the reproducibility of the results obtained using the methodology described, the trace to trace and breath to breath variation of data for each patient was assessed.

Breath to breath variation was expressed as the coefficient of variation (100 X standard deviation / mean) over a minimum of 3 breaths.

Trace to trace variation for each subject was calculated as the difference of each trace from the mean of 3 traces expressed as a percentage of the mean.

All calculations were done on computer using locally developed software or Quattro Pro (initially, but subsequently in Excel). Statistical analysis was performed using Statgraphics. Graphical display was performed using Statgraphics or Harvard Graphics.

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4.7.2 All other data

Statistical analysis was with Microsoft Excel 97™ (Microsoft Corporation, Redmond, WA, USA) and Analyse-it™ version 1.71 (Analyse-It Software Ltd, Leeds, UK). Specific tests used in the analysis are shown in the relevant chapters. A p-value <0.05 was assumed to be significant.

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Chapter 5
Results and discussion of evaluation of methodology

5.1 Results

5.1.1 Application of facemask

Application of the facemask (assessed on single baseline traces on patients with croup and controls) caused a variable change in ΔPoes in controls (median 3.5 cm H_2O, range: 0.9 – 10.5 cm H_2O) and in patients with croup (median 6.64, range: –22.9 – 47.3 cm H_2O) (table 5.1), although the increase appeared to be relatively larger in the normal group, (54% vs 29%).

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Table 5.1: Effect of facemask application

	Croup			**Normal**		
	Pre Mean (sd)	**Post Mean (sd)**	**p-value (paired student's t-test)**	**Pre Mean (sd)**	**Post Mean (sd)**	**p-value (paired student's t-test)**
Sample size	20	20		5	5	
Peak-to-trough ΔPoes (cm H_2O)	**61 (23.5)**	**70 (26.6)**	**0.02**	**10.5 (2.0)**	**15.1 (4.5)**	**0.048**
Respiratory rate (b/min)	39.1 (10.3)	40.6 (8.5)	0.23	29.8 (7.1)	30.6 (6.9)	0.59
Pressure-Rate Product (cm H_2O/min)	**2341 (935)**	**2756 (1017)**	**0.02**	**311 (85.1)**	**452 (129.4)**	**0.0008**

Any increase in peak-to-trough ΔPoes occurred within a few breaths of application of the mask. Thereafter there was no change in the peak-to-trough ΔPoes and the ΔPoes remained at that level. Although there was no significant change in

respiratory rate following mask application in either group the Pressure-Rate Product was significantly increased by application of the face-mask in both groups.

5.1.2 Occlusion studies

Attempts to perform occlusion-validation tests of ΔPoes in patients with croup, as recommended by Milner et al (257), were futile as children roused immediately and resisted.

5.1.3 Reproducibility of data

In general trace to trace variability was higher in patients with croup. Trace to trace coefficient of variation data is shown in table 5.3. Respiratory rate and flow volume data generally had a trace to trace variability of < 10% with the exception of peak and mid expiratory flow on patients with croup (10.77 and 12.33 respectively). Pressure data had more trace to trace variation with median coefficient of variation for peak inspiratory and expiratory pressure changes on croup and peak expiratory pressures on controls exceeding 10%. Trace to trace variation was higher in indices derived from flow-volume data with several of these measure exceeding median values of 10% in both croup and control patients. Only Tmif / Ti_{TOT} on normal controls exceeded 10% in the indices derived from the flow-volume data. Indices derived from flow-pressure data and indices of effort generally had median values of coefficient of variation of < 10%, with compliance in patients with croup being an obvious exception. However some patients had high trace to trace variability of data.

On indices derived from Flow-Pressure data, the trace to trace variability was high, particularly in terms of compliance.

Breath to breath variation is shown in Table 5.3. Breath to breath variation for respiratory rate and flow and volume data was generally low with median values all <10%. Peak inspiratory pressure change data had a relatively high breath to breath variability in normal controls (at least partially related to the relatively low values.

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Table 5.2: Trace to Trace Variability (expressed as coefficient of variation)

Variable	Normal	Croup	p-value (Mann-Whitney)
Sample size	5	10	
Respiratory rate data			
Respiratory rate	**1.86 (0.23 – 10.1)**	**4.87 (0.24 – 42.4)**	**0.0001**
Inspiratory time	**3.04 (0.89 – 7.39)**	**5.35 (0.48 – 23.6)**	**0.0093**
Expiratory time	2.21 (0.01 – 13.13)	4.14 (0.04 – 44.0)	0.067
IE ratio	3.35 (1.29 – 7.98)	3.15 (0.03 – 30.4)	0.36
Flow and volume data			
Peak inspiratory flow	6.01 (0.08 – 12.36)	8.16 (0.28 – 42,9)	0.09
Mid inspiratory flow	5.32 (0.07 – 14.7)	8.99 (1.02 – 51.48)	0.06
Peak expiratory flow	**4.27 (0.10 – 23.7)**	**10.77 (0.17 – 40.8)**	**0.016**
Mid expiratory flow	**4.92 (0.41 – 19.4)**	**12.33 (2.00 – 62.5)**	**0.002**
Tidal Volume	**2.62 (0.23 – 7.27)**	**5.27 (0.07 – 61.1)**	**0.047**
Pressure data			
Peak inspiratory Poes (cm H_2O)	**6.34 (0.14 – 16.3)**	**10.84 (0.28 – 48.3)**	**0.024**
Peak expiratory Poes (cm H_2O)	11.2 (0.42 – 23.9)	11.87 (0.79 – 49.4)	0.32
Peak to Peak Poes (cm H_20)	**4.81 (0.20 – 10.99)**	**8.85 (0.45 – 47.5)**	**0.047**
Indices derived from Flow-Volume data			
AFV (ml/s.ml/kg)	**5.6 (0.2 – 17.1)**	**12.21 (0.80 – 102)**	**0.002**
Tmif / Ti_{TOT} (%)	10.6 (1.36 – 81.9)	5.01 (0.05 – 44.9)	0.12
Tmef / Te_{TOT} (%)	6.1 (0.23 – 15.7)	7.99 (0.24 – 71.8)	0.055
Mid expiratory flow / mid inspiratory flow	7.36 (0.92 – 21.5)	5.81 (0.32 – 33.3)	0.479
Indices derived from Flow-Pressure data			
$R_{AW}0.5_I$ (cm H_2O/L/s)	**8.9 (2.2 – 26.5)**	**21.0 (2.24 – 63)**	**0.016**
$R_{AW}0.5_E$ (cm H_2O/L/s)	12.01 (0.19 – 28.1)	16.7 (1.07 – 62.9)	0.055
Compliance (ml/cm H_2O/kg)	**15.0 (1.5 – 45.5)**	**65.5 (1.8 – 170)**	**0.0001**
Indices of effort			
Pressure-Time Integral (cm H_2O.s/min)	7.6 (1.97 – 17.3)	7.20 (0.24 – 48.4	0.87
Work of breathing (gm.cm/kg)	6.9 (0.5 – 26.1)	12.34 (0.01 – 87.9)	0.12
Rate of work of breathing (gm.cm/min/kg)	**7.02 (0.08 – 23.8)**	**16.5 (0.16 – 72.1)**	**0.0093**
Volume for Effort (ml/cm H_2O/s)	**6.82 (2.0 – 23.8)**	**12.3 (2.7 – 58.8)**	**0.038**

All data as median (range)

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Table 5.3: Breath to breath Variability (expressed as coefficient of variation) from baseline studies

Variable	Normal	Croup	p-Value (Mann Whitney)
Sample size	5	20	
Respiratory rate data			
Inspiratory time	0.78 (0.75 – 2.73)	1.68 (0.38 – 3.89)	0.12
Expiratory time	1.70 (0.91 – 2.47)	2.0 (0.58 – 5.51)	0.34
Flow and volume data			
Peak inspiratory flow	1.91 (1.31 – 6.85)	3.7 (0.27 – 8.13)	0.38
Mid inspiratory flow	2.66 (1.42 – 6.45)	3.1 (0.89 – 17.2)	0.84
Peak expiratory flow	2.49 (0.28 – 5.55)	4.91 (1.16 – 9.03)	0.10
Mid expiratory flow	2.90 (1.06 – 6.69)	5.27 (1.15 – 16.9)	0.10
Tidal Volume	**3.20 (0.79 – 4.26)**	**5.54 (2.45 – 10.65)**	**0.004**
Pressure data			
Peak inspiratory Poes (cm H_2O)	3.55 (1.5 – 7.9)	3.8 (0.76 – 8.64)	0.89
Peak expiratory Poes (cm H_2O)	11.24 (1.05 – 27.3)	4.84 (1.34 – 11.5)	0.197
Indices derived from Flow-Volume data			
AFV (ml/s.ml/kg)	4.07 (2.28 – 7.48)	6.72 (1.18 – 13.6)	0.15
Tmif / Ti_{TOT} (%)	16.1 (8.77 – 29.3)	10.0 (2.48 – 42.0)	0.12
Tmef / Te_{TOT} (%)	12.03 (4.1 – 21.5)	12.9 (1.6 – 24.9)	0.84
Indices derived from Flow-Pressure data			
$R_{AW}0.5_I$ (cm H_2O/L/s)	5.68 (2.04 – 9.6)	7.04 (2.22 – 24.8)	0.31
$R_{AW}0.5_E$ (cm H_2O/L/s)	5.65 (3.1 – 8.9)	8.3 (0.95 – 21.4)	0.42
Compliance (ml/cm H_2O/kg)	**8.31 (5.52 – 14.5)**	**32 (7.4 – 76)**	**0.002**
Indices of effort			
Pressure-Time Integral (cm H_2O.s/min)	4.16 (1.08 – 5.02)	3.01 (0.45 – 5.94)	0.84
Work of breathing (gm.cm/kg)	6.88 (1.40 – 7.18)	6.01 (1.58 – 11.9)	0.50

Data expressed as median (range)

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Table 5.4: Results from normal control patients

Variable	Normal
Respiratory rate data	
Respiratory rate (b/min)	29.0 (22.4 – 43)
I:E ratio	0.93 (0.72 – 0.97)
Inspiratory time (s)	1.02 (0.66 – 1.30)
Expiratory time (s)	1.10 (0.74 – 1.39)
Flow and volume data	
Peak inspiratory flow (ml/s)	99.5 (78.5 – 146.5)
Mid inspiratory flow (ml/s)	96.3 (72.5 – 133.8)
Peak expiratory flow (ml/s)	108.8 (93.2 – 158.6)
Mid expiratory flow (ml/s)	103.8 (76.9 – 153.7)
Tidal Volume (ml/kg)	8.1 (7.6 – 10.2)
Minute Ventilation (ml/min/kg)	235.4 (214.9 – 324.5)
Pressure data	
Peak-to-trough ΔPoes (cm H_2O)	11 (7 – 12.5)
Peak inspiratory Poes (cm H_2O)	-11.9 (-7.4 - -21.6)
Peak expiratory Poes (cm H_2O)	1.9 (1.6-3.9)
Indices derived from Flow-Volume data	
AFV (ml/s.ml/kg)	1594 (1442 – 1953)
Tmif / Ti_{TOT} (%)	61.2 (16 -66.9)
Tmef / Te_{TOT} (%)	32.0 (21.1-62.9)
Mid expiratory flow / mid inspiratory flow	1.15 (0.8-1.4)
Indices derived from Flow-Pressure data	
$R_{AW}0.5_I$ (cm H_2O/L/s)	101.2 (63.8 – 201.6)
$R_{AW}0.5_E$ (cm H_2O/L/s)	12.5 (3.0 – 32.5)
Compliance (ml/cm H_2O/kg)	1.18 (0.64-2.1)
Indices of effort	
Pressure-Rate Product (cm H_2O/min)	312 (196 – 430)
Pressure-Time Integral(cm H_2O.s/min)	299 (197 – 537)
Work of breathing (gm.cm/kg)	81 (47 - 115)
Rate of work of breathing (gm.cm/min/kg)	2597 (1370 – 2279)
Volume for Effort (ml/cm H_2O/s)	7.33 (4.6 – 11.86)

All data as median (range)

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5.1.3 Normal control patients

Traces from normal control patients are shown in Chapter 6 in contrast to traces from patients with croup. Measured and derived parameters are shown in table 5.4.

5.2 Discussion

5.2.1 Patient groups

During the period 1990 to 1995 1525 patients with croup were admitted to the Red Cross War Memorial Children's Hospital with a diagnosis of croup. The children ranged in age from 2 days to 20 years, but the mean age was 17.5 months. Of these children 439 (29%) were admitted to the intensive care unit and the mean age was 15.4 months (range 2-120 months). Thus the children in this study (both control and croup) were within the usual age-group although slightly younger than the majority of children.

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5.2.2 Application of the facemask

The increase in respiratory effort associated with application of the mask was very rapid and thus probably related to stimulation of the trigeminal nerve (270,272) and not to the increased resistance. There was not a progressive increase in respiratory effort as would be expected if increased deadspace from the facemask (276) was responsible for the increased effort. In addition the shape of the pressure traces did not change with application of the facemask suggesting that essential elements of the respiratory pattern were not affected.

Schulzke et al (302) looked at the effect of nasal vs. face masks for the evaluation of lung functions in premature infants. There was no difference in lung functions using either system (both of which had bias flow systems in place to reduce dead space. They commented on the complexity of the deadspace measurement. The volume of the mask and pneumotachograph will be reduced by the face during application. In addition air flow may only go through some of the mask and so again, the volume of

the mask and pneumotachograph space may not reflect the effective deadspace of the apparatus.

The problems associated with application of the facemask, imply that it might be better to either find measures of respiratory mechanics which do not require measurement of air flow and / or tidal volumes, or to use alternative methodologies for measurement of flow and tidal volume. Body-box methodology would be difficult to use safely acutely ill children, however respiratory impedance tomography may be an appropriate alternative approach. Habib et al (303) have shown that comparable results can be obtained using pneumotachographs and respiratory impedance plethysmography in small infants. Likewise Sivan et al (125) were able to measure tidal volumes in a group of children with upper airway obstruction.

5.2.3 Occlusion studies

Unfortunately it was not possible to use the occlusion test as a means of ensuring that oesophageal catheter placement was ideal in each patient. Attempts to perform occlusion-validation tests of ΔPoes in patients with croup, as recommended by Milner et al (257), were futile as children roused immediately and resisted. This is potentially a problem when comparing individual patients, but probably not significant when following the responses of an individual patient to therapy.

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5.2.4 Data from normal control patients.

The peak inspiratory ΔP of 12.7 cm H_2O in the control patients is higher than the 7.3cm H_2O reported by Gerhardt et al (304). This gives rise to an inspiratory resistance which is higher than expected and also higher than the expiratory resistance when the reverse would be expected (305)

Possible reasons for this include: the extra dead space of the mask (20-25ml relative to the 0.5-1.0ml in the system employed by Gerhardt) (304); the facial stimulation related to facemask application as discussed previously (nasal prongs were used by Gerhardt et al) (272); the nasal obstruction related to the used of an 8FR nasogastric

tube. The resistance of the pneumotachograph - facemask assembly was insignificant.

Patzak et al have demonstrated that on lung function testing on infants (306), the tidal volume reduced in the period after the first minute of mask application. In all our patients the mask was applied for <1 minute only.

The naso-oesophageal tube may have increased the upper airways resistance (307) and this may explain the inspiratory resistance of the normal patients being higher than the expiratory resistance, when the reverse would be expected (308). Greenspan et al (307) demonstrated that while in neonates of over 2 kg of weight the presence of a 5FR nasogastric tube made no difference to pulmonary resistance, in smaller infants (<2kg) it made a significant contribution to pulmonary resistance. Thus the 8FR catheter used in this study may have contributed to higher than expected pulmonary resistance. Unfortunately use of a 5Fr catheter was associated with unacceptable distortion of the signal.

Flow and tidal volumes are within the range reported in previous studies (309-312). Tidal volumes and minute ventilation from studies on normal infants are shown in table 5.5. The tidal volumes recorded in our normal patients were higher than those in other studies quoted above. However there are very few studies which have studied infants of comparable age - most studies having focussed on neonates and premature infants. The stimulation of the facemask application (as discussed previously) may be a factor in this increase in tidal volume.

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Table 5.5: Reported Tidal volumes and Minute ventilation

Author	**Patient group**	**Mean Tidal volume (ml/kg)**	**Mean Minute Ventilation (ml/min/kg)**
Greenspan et al (307)	Neonates greater than 2kg	Not available	376
Sivan et al (125)	Croup	4.4	Not available
Gerhardt et al (304)	Normal infants and children up to age 5 years (16 were studied in the neonatal period and 24 thereafter)	6.9 (± 1.4)	
Marsh et al (276)	Neonates	5.2 (biased flow reduced this to 4.9)	284 (biased flow reduced this to 220)
Davis et al (313)	Premature infants	7.78	442
Schulzke et al (302)	20 newborn infants with mean weight of 2kg (mean gestational age 31w) and clinically stable. (volume corrected on mean weight)	6.4 when measured with facemask	399.6
Schmalisch et al (314)	Normal controls in comparison to infants with chronic lung disease	5.57 ±1.06	215 ± 51.7
Schmalisch et al (315)	Normal neonates – paper looking at effect of through flow vs deadspace	6.1 ± 1.5	349±97
Latzin et al (316)	Group of healthy term	7.5+1.4	328+65

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	infants at approximately 35 days of life. Part of a control group in a study of preterm infants		
Lødrup et al (309,310,312,317)	803 healthy full term neonates	6.95 (calculated from mean tidal volume and mean weight)	
Patzak et al (306)	14 healthy newborn infants	5.5±1.1	233±93
Turner et al (236)	Normal infants	7.17	354
This study	**Normal infants**	**8.1 (7.6 – 10.2)**	**235.4 (214.9 – 324.5)**

Similarly data on the parameter $Tmef/Te_{TOT}$ is similar to that previously reported in studies including normal infants (310,312).

The equipment used in this study to analyze flow and flow volume data is suboptimal as described by Bates et al (318), but as will be seen later is adequate to demonstrate significant differences between normal controls and patients with croup. It would be optimal for these studies to be repeated with more sophisticated equipment.

The comparison of pulmonary resistance data with published data is complicated by the multitude of methods used to arrive at the results. Some previously published results are shown in the following table arranged by the methods of measurement used.

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Table 5.6: Reported normal resistance data

Author	Age-group	Mean	Range
Mid-inspiratory airways resistance (cm H_2O/L/s)			
Swyer (319)	Newborn	26	9 to 54
Krieger (297)	3 weeks to2 years	37	4 to 111
Mid-expiratory airways resistance (cm H_2O/L/s)			
Krieger (297)	3 weeks to 2 years	22	5 to 64
Gerhardt et al (304)	0 to 5 years	55	18 to 136
Respiratory resistance ($\Delta P/(Flow_{insp} + Flow_{exp})$			
Krieger (297)	< 2 years	20	4 to 80
Cook et al (320)	Neonates	29	7 to 131
Polgar and Kong (321)	Neonates	47.5	38 to 53
Airways resistance (Plethysmography)			
Stocks et al (322)	Infants	35.6	13.9 to 52.3

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Beardsmore et al (305) published data on airway resistance (Raw) measured using a plethysmograph and rebreathing apparatus during tidal respiration in 15 infants. This methodology allowed correction for apparatus resistance at each point of the respiratory cycle. They found that there was substantial variation in the Raw during tidal breathing, and that although the relationship between Raw and flow was complex, Raw was relatively stable during the mid tidal volume range. In 3 subjects with normal SGaw, maximum inspiratory and expiratory Raw were 22, 32, 43 and 36, 25, 42 cm H_2O/L/s respectively.

The values obtained for pulmonary resistance in our normal subjects were somewhat higher than the mean but within the ranges reported in other studies.

5.3 Conclusions

The data has thus shown that both the croup and control patients were within the population that is generally admitted to the Red Cross War Memorial Children's hospital with acute severe croup, and are thus to some extent representative. Control patients were within the same age and size group and were thus reasonable controls for this study (although limited in number).

For most of the parameters assessed in this study, was reasonably reproducible in terms of breath to breath variation and in terms of trace to trace variation.

The data obtained from control patients was comparable with normal data previously obtained in a variety of studies of the mechanics of breathing in children of comparable age. However there are concerns regarding the possible impact of the application of the face mask (direct effect and deadspace), as well as the effects of the nasogastric tube inserted in all patients. The equipment utilized for measurement of lung functions was not ideal from the perspective of lung function assessment, but was practical in terms of the equipment available at the hospital, and in many hospitals which treat patients with croup. Further studies with optimized equipment may be both informative and beneficial.

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Chapter 6:
Baseline croup and normal control data

6.1 Results

All croup and control patients had oxygen saturations greater than 92% in room air during these studies. All results are tabulated, along with statistical probabilities, in Tables 6.1 and 6.2. Although a p value of <0.05 was accepted as statistically significant, it is important to note that while p values for parameters associated with oesophageal pressure changes were all <0.01, only p values for Tidal Volume and Tmef / Te_{TOT} were <0.01.

6.1.1 Respiratory rate data (see table 6.1)

The respiratory rate of patients with croup was significantly higher than that of controls. Because croup cases breathed faster, both inspiratory and expiratory times were shorter in croup but the inspiratory to expiratory time ratios (I:E) remained the same as in controls.

6.1.2 Flow and volume data (see Table 6.1)

Inspiratory flow rates in croup and controls were equivalent, for both peak and mid-inspiratory flows.

Peak expiratory flow was about 25% less in croup than controls, and mid-expiratory flow was lower in croup although this difference did not reach statistical significance. However, reduction in expiratory flow rates in croup resulted in a significant decrease in the ratio of mid-expiratory to mid-inspiratory flow.

Tidal flow volume analysis showed that the Tmef / Te_{TOT} (%) was increased in patients with croup. There were no differences in Tmif / Ti_{TOT}. Area within the flow-volume curve was significantly decreased in patients with croup.

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Compared with controls, children with croup had lower tidal volumes but breathed faster, thus maintaining similar minute volumes.

6.1.3 Pleural (Oesophageal) pressure data

For patients with croup there was a correlation between age and ΔPoes ($r = 0.65$, $p = 0.002$), and this correlation held for PRP ($r = 0.52$, $p = 0.018$), and PTint ($r = 0.59$, $p = 0.007$). The relationship did not hold for either height or weight.

Peak-to-trough pleural pressure swings (ΔPoes) measured without the facemask in place, were five times higher in croup than controls. Peak-to-trough pleural pressure changes were large in patients with croup with a range of 27 to 120 cm H_2O. Most of the pressure swings occurred during inspiration with median peak inspiratory pressure changes of 47.6 cm H_2O (range 12.6 to 92.8 cm H_2O) in patients with croup vs. 11.9 cm H_2O (range 7.4 to 21.6 cm H_2O) in controls. (Table 6.1, Figs 6.2 and 6.3)

The indices of effort derived from oesophageal pressure measurements were also elevated. The Pressure-Rate Product (PRP) was 7-fold higher and the PTint 5-fold higher in croup than in controls.

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Table 6.1: Respiratory mechanics data

Variable	Normal	Croup	Mann Whitney p-value
Sample size	5	20	
Croup score	0	3 (2-3)	
Respiratory rate data			
Respiratory rate (b/min)	**29.0 (22.4 – 43)**	**38.2(29.5 - 59.7)**	**0.02**
I:E ratio	0.93 (0.72 – 0.97)	0.86 (0.63 – 1.03)	0.25
Inspiratory time (s)	**1.02 (0.66 – 1.30)**	**0.73 (0.46 – 0.96)**	**0.03**
Expiratory time (s)	**1.10 (0.74 – 1.39)**	**0.86 (0.51 – 1.07)**	**0.02**
Flow and volume data			
Peak inspiratory flow (ml/s)	99.5 (78.5 – 146.5)	99.7 (55.1 – 159.4)	0.79
Mid inspiratory flow (ml/s)	96.3 (72.5 – 133.8)	94.5 (53.0 – 146.7)	0.95
Peak expiratory flow (ml/s)	**108.8 (93.2 – 158.6)**	**88.7 (44.6 – 185.3)**	**0.03**
Mid expiratory flow (ml/s)	103.8 (76.9 – 153.7)	80.8 (41.8 – 180.8)	0.06
Tidal Volume (ml/kg)	**8.1 (7.6 – 10.2)**	**5.5 (2.8 – 13.1)**	**0.005**
Minute Ventilation (ml/min/kg)	235.4 (214.9 – 324.5)	209.5 (98.3 – 506.4)	0.20
Pressure data			
Peak-to-trough ΔPoes (cm H_2O)	**11 (7 – 12.5)**	**58 (27 – 120)**	**< 0.001**
Peak inspiratory Poes (cm H_2O)	**-11.9 (-7.4 - -21.6)**	**-47.6 (-12.6 - -92.8)**	**< 0.001**
Peak expiratory Poes (cm H_2O)	**1.9 (1.6-3.9)**	**23.5 (5.18-36.3)**	**< 0.001**
Indices derived from Flow-Volume data			
AFV (ml/s.ml/kg)	**1594 (1442 – 1953)**	**797 (243 – 3924)**	**0.01**
Tmif / Ti_{TOT} (%)	61.2 (16 -66.9)	62.9 (36.7 – 83.1)	0.73
Tmef / Te_{TOT} (%)	**32.0 (21.1-62.9)**	**72.8 (48.7-91.4)**	**0.004**
Mid expiratory flow / mid inspiratory flow	**1.15 (0.8-1.4)**	**0.8 (0.6-1.23)**	**0.02**
Indices derived from Flow-Pressure data			
$R_{AW}0.5_I$ (cm H_2O/L/s)	**101.2 (63.8 – 201.6)**	**428.4 (141.9 – 825.8)**	**0.001**
$R_{AW}0.5_E$ (cm H_2O/L/s)	**12.5 (3.0 – 32.5)**	**222.2 (21.7 – 433.9)**	**0.001**
Compliance (ml/cm H_2O/kg)	**1.18 (0.64-2.1)**	**0.46 (0.11 – 2.5)**	**0.035**
Indices of effort			
Pressure-Rate Product (cm H_2O/min)	**312 (196 – 430)**	**2120 (680 – 4320)**	**< 0.001**
Pressure-Time Integral (cm H_2O.s/min)	**299 (197 – 537)**	**1618 (358 – 2298)**	**< 0.001**
Work of breathing (gm.cm/kg)	**81 (47 - 115)**	**293 (77 - 1163)**	**< 0.001**
Rate of work of breathing (gm.cm/min/kg)	**2597 (1370 – 2279)**	**9919 (3014 – 43093)**	**< 0.001**
Volume for Effort (ml/cm H_2O/s)	**7.33 (4.6 – 11.86)**	**1.61 (0.95 – 5.59)**	**< 0.001**

(All values expressed as: Median (range)

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6.1.4 Data derived from flow and pleural pressure data

During inspiration all but 2 croup cases (but no controls) displayed flow-limitation (Figures 6.2 and 6.3). The 2 patients with croup that did not demonstrate flow limitation were clinically assessed as having airway obstruction (one Grade 2 and the other Grade 3). Their objective measures of airway obstruction showed mid-inspiratory resistance ($R_{AW}0.5_I$) of 142 and 270 cm H_2O/L/s. The lower value was the lowest inspiratory resistance recorded in our series of patients with croup (Table 2) and the value of 270 cm H_2O/L/s was also fairly close to the highest value recorded in our normal subjects, reflecting milder disease.

Expiratory flow-limitation was not observed in either patients with croup or controls, but in 4 cases of croup we observed fluctuations in exhaled flow rates without concurrent changes in oesophageal pressure a phenomenon we believe represents glottic braking. As depicted in the figures there were different patterns of glottic braking.

Mid-inspiratory resistance was increased about 4-fold and peak expiratory resistance 9-fold in patients with croup compared with controls. Respiratory system compliance was significantly decreased from controls.

The increase in Work of Breathing was similar to that of the increase in PTint.

VFE highlighted the major differences between patients with croup and normal controls, in that the minute ventilation for effort expended was nearly 4.5 times higher than that in normal controls.

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Figure 6.1: Normal subject – no flow limitation

Normal Subject Flow and Pressure Curves plotted against Time

From the beginning of inspiration, as pressure decreases to its maximum but modest negative value, flow increases significantly up to the point marked by the solid arrows. Thereafter, there is a decline in negative pressure as flow continues unchanged. During expiration, very modest increases in pressure are associated with relatively high flows (open arrows). There is no evidence of flow limitation. ΔPoes is approximately 13 cm H_2O.

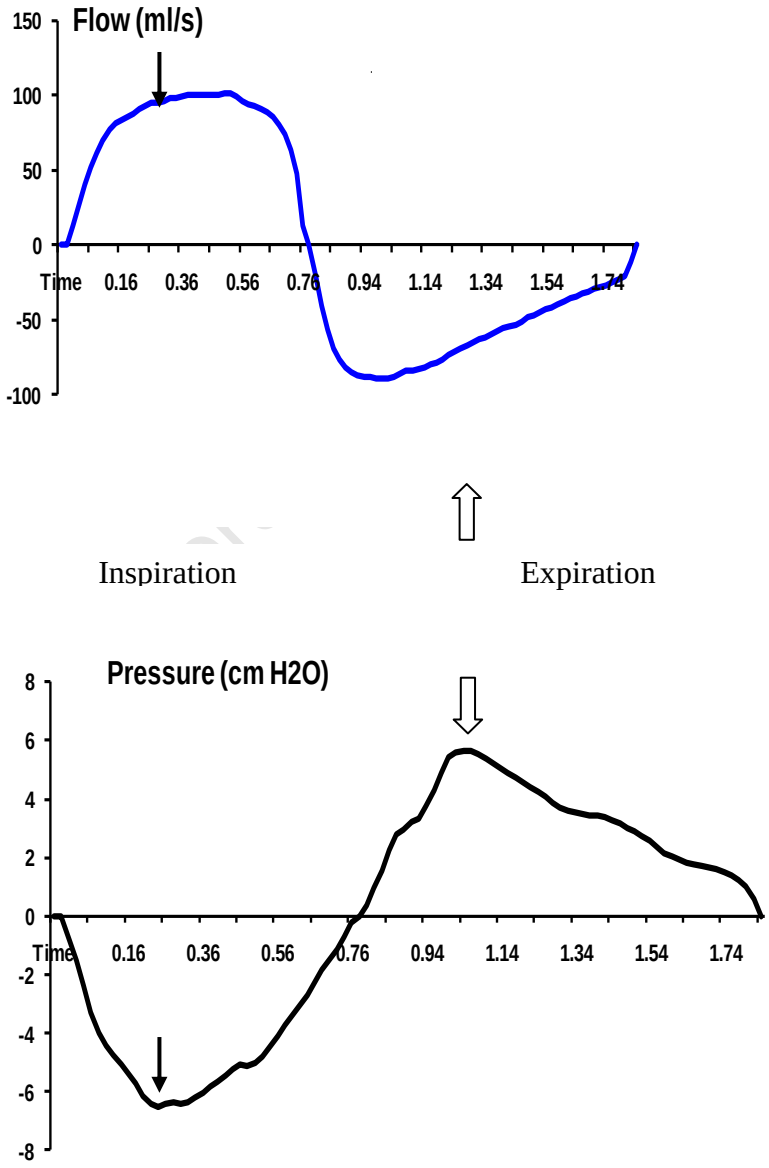


Figure 6.2: Croup patient - flow limitation

Croup Patient Flow and Pressure Curves plotted against Time

Traces demonstrating inspiratory flow limitation. During initial inspiration there is a positive increase in inspiratory flow associated with a change in oesophageal pressure (left of solid arrow). To the right of the arrow, until shortly before expiration begins, there is no further increase in inspiratory flow despite a large increase in negative pressure. This represents inspiratory flow limitation. During expiration, there is no evidence of flow limitation but oesophageal pressure is higher and flows are less than seen in the normal subject (Figure 6.1). ΔPoes is approximately 70 cm H_2O.

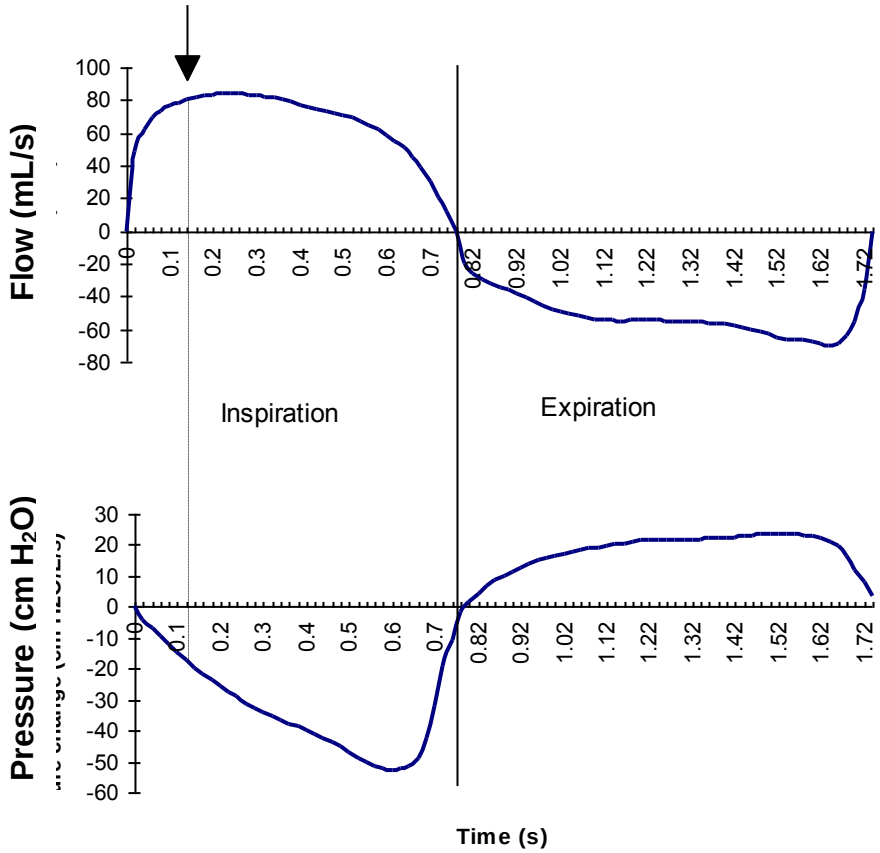


Figure 6.3: Pressure-Flow Plots for a normal subject and a croup patient

Oesophageal pressure plotted against flow for:

A. Normal subject: During inspiration, as the intrathoracic (oesophageal) pressure drops modestly, flow increases markedly. Expiration is also associated with high flows with little pressure generation required to achieve them.

B. Croup patient: Initially during inspiration, the oesophageal pressure decreases and there is a rapid increase in flow (arrows **a** to **b**). Thereafter (arrows **b** to **c**), there is a large change towards very negative pressures (compared with the normal subject) with only a very small increase in flow. This is a demonstration of inspiratory flow limitation. During exhalation, reasonable flows are achieved but only with more positive intrathoracic pressure generated compared with the normal subject.

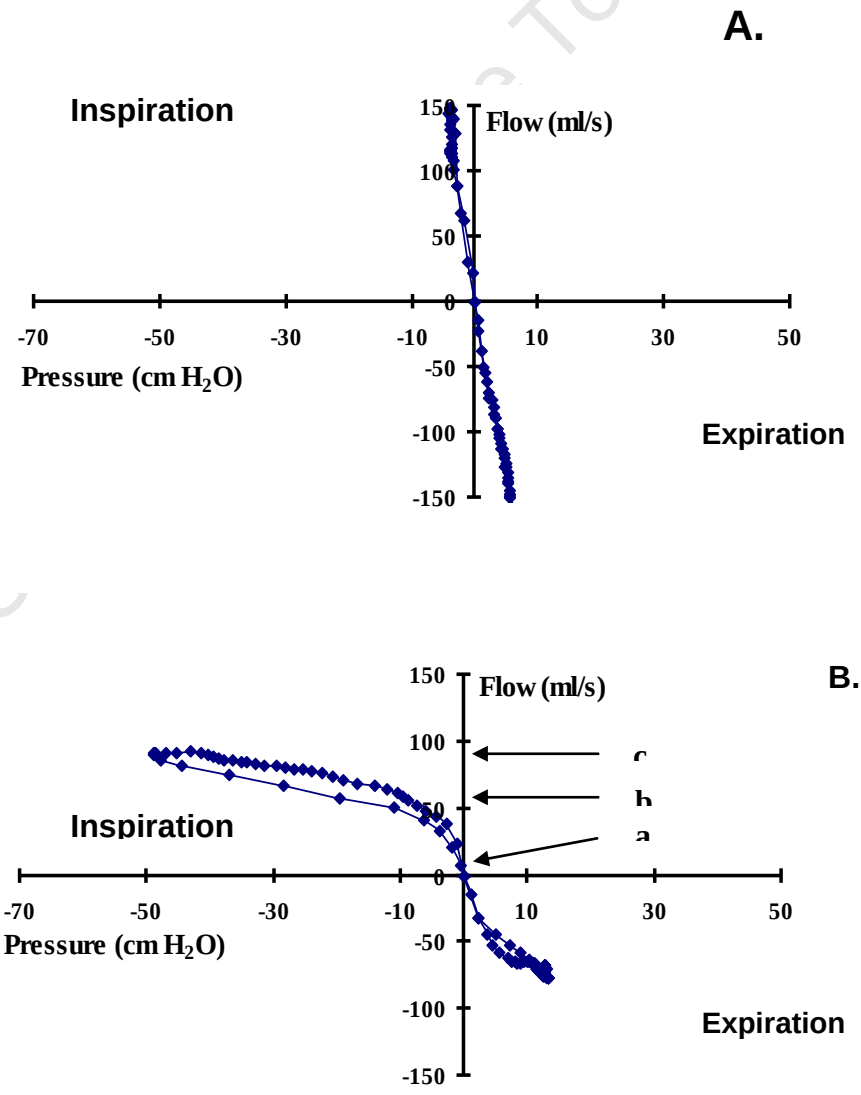
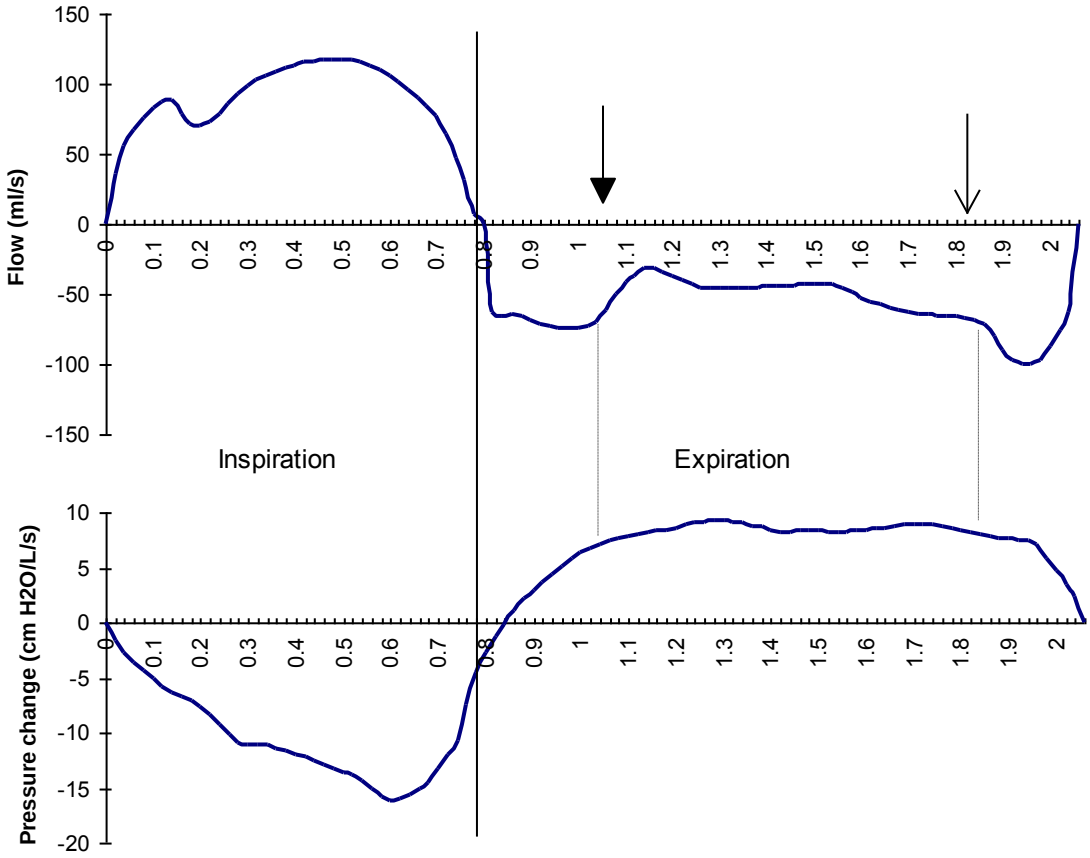


Figure 6.4: Expiratory glottic braking

This is example of expiratory glottic braking. In this example there is a sudden drop in expiratory flow (marked with closed arrow) which then increases again (marked with open arrow) with no associated changes in pressure. This relates to closure and subsequent reopening of the glottic aperture.



6.1.5 Effect of Endotracheal Intubation (see Table 6.2)

Following endotracheal intubation, indices of airway obstruction and effort improved and both inspiratory and expiratory airways resistance returned to the range of normal controls (the level of statistical significance was placed at <0.01 given the small number of patients).

The values for $R_{AW}0.5_E$ following intubation were similar to controls, suggesting that small airways obstruction is not a significant factor in croup. Respiratory system dynamic compliance improved but remained less than that of normal control children.

VFE improved substantially following intubation, as did PRP and PTint. WOB and Rate of WOB declined substantially but not statistically significantly. Peak inspiratory and expiratory oesophageal pressures, along with peak-to-trough pressure changes, also declined although this did not reach statistical significance at the level of <0.01.

Respiratory rates and measures of flow and tidal volume did not change significantly following intubation. However, tidal flow-volume loop analysis showed significant changes in time to peak expiratory flow / expiratory time while the area within the flow-volume loop approached statistical signficance.

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Table 6.2: Effect of intubation

	Before Mean (SD)	After Mean (SD)	Change (%)	Paired t-Test
Sample size	4	4		
Respiratory Rate Data				
Respiratory Rate (b/min)	35.8 (5.9)	36.4 (9.0)	-2	0.92
Flow and volume data				
Peak inspiratory flow (ml/s)	105 (25.7)	141 (35.5)	+34	0.02
Mid inspiratory flow (ml/s)	**99 (24)**	**128 (26.8)**	**+29**	**0.009**
Peak expiratory flow (ml/s)	85 (25)	123 (55)	+45	0.195
Mid expiratory flow (ml/s)	79 (25)	110 (48)	+39	0.202
Tidal volume (ml/kg)	5.1 (0.85)	6.2 (0.89)	+22	0.06
Minute ventilation (ml/kg/min)	182 (30)	223 (42)	+23	0.13
Pressure data				
Peak-to-trough ΔPoes (cm H_2O)	76 (34)	24 (7)	-68	0.04
Peak inspiratory Poes (cm H_2O)	-57 (28)	-20 (8.7)	-65	0.04
Peak expiratory Poes (cm H_2O)	19 (6.5)	3.6 (2.6)	-81	0.04
Indices derived from Flow-Volume data				
AFV (ml/s.ml/kg)	868 (378)	1367 (561)	+58	0.02
Tmif / Ti_{TOT} (%)	65 (4.6)	73 (3.9)	+12	0.14
Tmef / Te_{TOT} (%)	**66 (21)**	**26 (8.9)**	**-61**	**0.005**
Mid expiratory flow / mid inspiratory flow	0.8 (0.15)	0.85 (0.24)	6.3	0.69
Indices derived from Flow-Pressure data				
$R_{AW}0.5_I$ (cm H_2O/ml/s)	349 (162)	87 (10)	-75	0.05
$R_{AW}0.5_E$ (cm H_2O/ml/s)	307 (65)	79 (17)	-74	0.003
Compliance (ml/cm H_2O/kg)	0.56 (0.43)	0.77 (0.2)	+38	0.40
Indices of Effort				
Pressure-Rate Product (cm H_2O/min)	2708 (1139)	899 (425)	-66.8	0.04
Pressure-Time Integral (cm H_2O.s/min)	1360 (628)	426 (130)	-68.7	0.05
Work of Breathing (gm.cm/kg)	283 (185)	105 (38)	-62.9	0.10
Rate of work of breathing (gm.cm/min/kg)	9934 (5833)	3890 (1843)	-60.8	0.099
Volume for Effort (ml/cm H_2O/s)	**1.67 (0.29)**	**6.22 (0.75)**	**+272**	**0.002**

All values expressed as: Mean (SD)
Statistical significance taken at the level of <0.01 and shown in bold.

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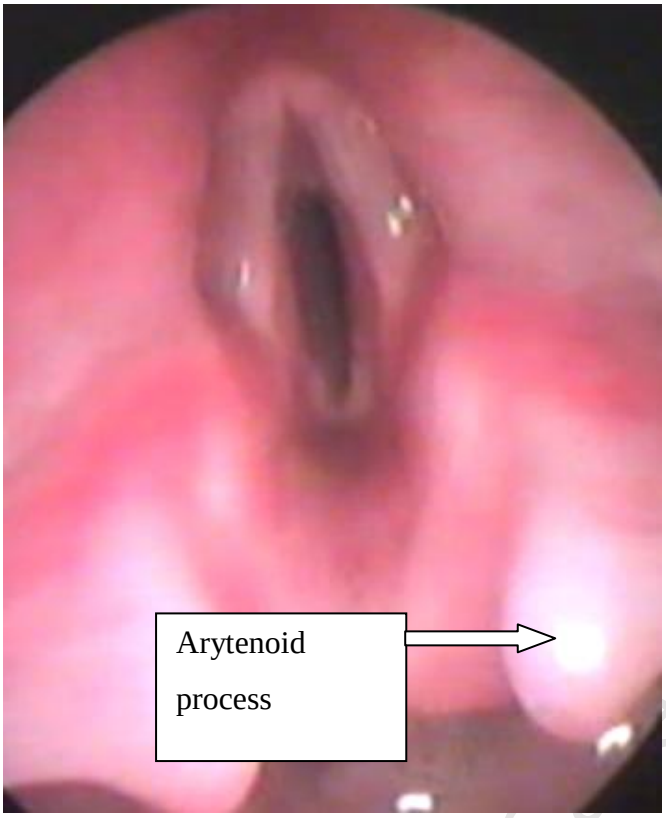
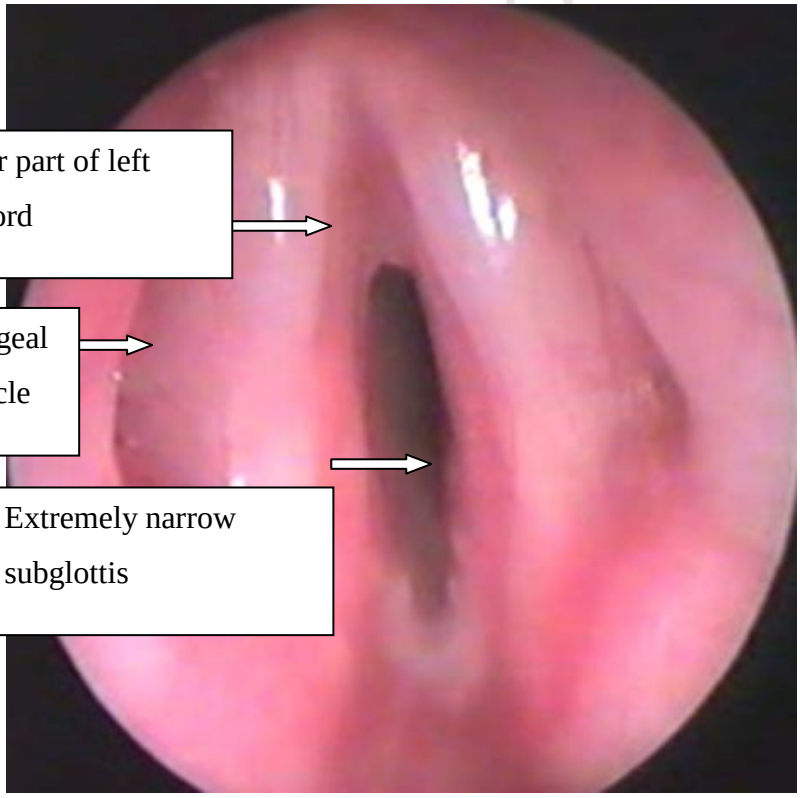
Figure 6.5: Endoscopic images from patient with acute severe croup



View of the larynx showing the laryngeal inlet with the arytenoids posteriorly



View showing the laryngeal inlet, with laryngeal ventricles, oedematous vocal cords and slit-like subgottis

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Slightly further into the larynx (now below the vocal cords, showing the severe side-to-side narrowing of the subglottis

View below the subglottis showing how the trachea is substantially larger in all dimensions than the subglottis

6.2 Discussion

Physiological measurements were obtained after sedation with chloral hydrate, as was the usual practice in our intensive care unit. Sedation of such patients is not unusual in this setting and has not been shown to cause any clinical deterioration (137).

6.2.1 Flow data

Flow and tidal volume data on normal controls are at the high end of reported data from neonates and normal infants (302,304,315,323), and this may reflect the stimulatory effect of face-mask application (see Chapter 5).

Flow and tidal volume data in patients with croup are similar to that recorded previously in patients with upper airway obstruction (including 5 patients with croup) by Sivan et al (mean 4.4ml/kg before treatment with adrenaline and 5.7ml/kg after treatment) (125), and patients with severe laryngotracheobronchitis (range approximately 6 to 16ml/kg) by Davis and co-workers (138).

It was not possible to differentiate between croup and normal cases on the basis of peak inspiratory and expiratory flow values. Peak expiratory flow rate was lower in patients with croup, but there was considerable overlap between normal control subjects and patients with croup. However, it is clear from the oesophageal pressure data that the flows achieved in patients with croup occurred at near maximal respiratory effort, while controls were breathing with minimal respiratory effort.

Flow limitation is the term applied to the phenomenon manifested when there is progressively increasing driving pressure (ΔPoes) without an associated increase in flow (Figures 6.2 and 6.3). Inspiratory flow limitation was consistently observed in 18 of 20 cases of croup but in no control subjects. This pattern is diagnostic of upper airway obstruction but is not specific to croup. For example, it has also been shown to occur in supraglottic obstruction in infants with laryngomalacia (305)

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There are a number of possible explanations for the inspiratory flow limitation, some of which may operate concurrently: 1) there is a "critical orifice" or choke point effect at the subglottis (324); 2) there is turbulence in the airway which may limit flow (325); 3) a combination of these 2 mechanisms (326); and 4) the extra-thoracic airways narrow during inspiration, due to dynamic compression (134), which adds to the resistance at the subglottis.

In a study of X-rays taken on 20 patients with croup, Jaroslawski (327) showed that the average side to side and antero-posterior dimensions of the subglottis were 1.0mm and 6.2mm respectively with minimum values of 0.3 and 4.8mm. This is in keeping with the images shown in figure 6.5.

Narrowing of the trachea at the cervico-thoracic junction during inspiration in infants with upper airway obstruction has been demonstrated on cineradiography (147). Narrowing of the anteroposterior diameter of the extrathoracic trachea by 61% during inspiration in croup (145) and a 58% reduction in tracheal cross-sectional area during inspiration in a patient with laryngomalacia (146) have also been demonstrated radiologically.

In a Master's thesis, Jaroslawski (327) used flow data from this study, together with measurements of airway dimensions in croup (taken from X-rays of children with croup) to demonstrate that it was highly likely that wave-speed flow limitation (with turbulent flow) was taking place in the subglottis of patients with acute severe croup. Using the wave speed theory of flow limitation he found a significant correlation between calculated maximum and actual maximum flow rates in children with acute severe croup.

Inspiratory time was not prolonged in patients with croup despite the inspiratory flow limitation and the I:E ratio was very similar to that seen in the normal controls.

Decreased expiratory flow rates in spontaneously breathing patients with croup could not be explained by increased small airways obstruction, as the resistance to flow did not increase during expiration. In addition, the patients who were studied after intubation did not show evidence of significant small airways disease once their

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upper airway obstruction was bypassed. In a group of 5 children intubated for measles related croup in 1992, Ross et al (328) reported pulmonary function findings of mildly increased airways resistance using a passive deflation technique under neuromuscular blockade. These measurements were made before extensive familiarity with normal controls with endotracheal tubes and it was later appreciated that the values obtained were within normal limits for intubated patients of this age and did not represent any distal airways disease (Newth CJL, personal communication). As in the current report, respiratory system compliance was reduced.

The decreased expiratory flows in spontaneously breathing patients with croup could be explained by at least two mechanisms. The first involves a combination of resistance from subglottic narrowing and expiratory glottic braking. Glottic braking or "grunting" has previously been described in association with hyaline membrane disease (329), and may be a means of maintaining normal lung volumes. An expiratory pattern very similar to that in figure 6.4 is shown in a study of grunting in low-birthweight infants (330). The intermittent presence of different patterns of expiratory glottic braking in patients with croup suggests that the glottis may be responsible for the control of expiratory flow in at least some patients with croup. In addition, this pattern was never observed in our patients after the glottic structures had been bypassed by endotracheal intubation.

Alternatively, some of the patterns that we have described as expiratory glottic braking could have been caused by retained secretions interfering with expiratory flow. However these patterns, when present, were consistent over periods of minutes which make secretions a less likely explanation. Another explanation could be that of increased inspiratory activity of the diaphragm into the (early) expiratory phase. During the latter phase of exhalation the abdominal muscles then contract to provide active expiration which is commonly clinically observed in severe croup. However, the traces show that there is no expiratory flow despite the presence of a significant intrathoracic driving pressure for expiration. That can best be explained by closure of the glottis.

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The time taken to peak expiratory flow as a proportion of expiratory time was increased in patients with croup. In patients with small airways disease, this proportion has been decreased (285) although the relationship of time to maximum expiratory flow as a proportion of expiratory time may be complex (288).

The area within the flow volume loop has previously been described in the context of a forced expiratory manoeuvre (293). However, we found the tidal AFV provided good differentiation between patients with croup and control subjects and possibly holds potential as a non-invasive measure of croup severity.

After intubation, while inspiratory flows increased significantly there were no significant changes in expiratory flows or tidal volumes.

6.2.2 Pressure data

The only previous data on intrathoracic pressure changes during airway obstruction from croup come from one intratracheal pressure tracing taken 3 days after acute presentation on a child who underwent a tracheotomy for severe croup (142). In this study, mean inspiratory pressures of –37 cm H_2O (range -24 to 50 cm H_2O) and mean expiratory pressures of 11 cm H_2O (range 5 –15 cm H_2O) were obtained following removal of the tube. This compares with 2 patients presenting in congestive heart failure from severe nasopharyngeal obstruction, in whom respiratory fluctuations of 0 - 18 mmHg (0 – 24.5 cm H_2O) were seen in pulmonary artery pressures during cardiac catheterizations (143).

All but 2 of the patients in this study had palpable pulsus paradoxus present during the study (Grade 3 or higher by clinical score), similar to patients with severe croup described by Steele et al (118). The 18 patients who displayed clinically palpable pulsus paradoxus had oesophageal pressure peak-to-trough swings ranging from 27 – 120 cm H_2O.

Experimental work in dogs (331) has shown that lower inspiratory intrathoracic pressures related to inspiratory airway obstruction were associated with an increase in left ventricular afterload, and the consequent development of pulsus paradoxus

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(332). Significant shifts of the interventricular septum with associated pulsus paradoxus have been shown in adults (332) and children (333) with severe oropharyngeal obstruction during sleep. The inspiratory pressure changes recorded in those studies were similar to or lower than pressure changes demonstrated in this study.

It is notable that, although there was a wide variation in measured dynamic compliances, patients with severe croup had significantly lower dynamic compliance than controls. This could reflect infective lung disease, increased lung water, or both. A number of authors have suggested that large intrathoracic pressures swings associated with upper airway obstruction may be implicated in the development of post-obstructive pulmonary oedema (334-336). Previously, it had been suggested that pulmonary oedema may develop in children with acute severe asthma as a result of negative intrapleural pressures (mean pleural pressures of down to -25.5 cm H2O) measured using oesophageal balloons (337). Mellins et al (338) had previously published animal data showing that negative intrapleural pressures were associated with increases in interstitial water collection. However, in another experimental model also using dogs, Polanski et al were unable to confirm these findings even after the dogs had generated pleural pressures of between -16 and –30 cm H_2O for variable periods of time.

The product of pleural pressure change and the associated tidal volume change provides the traditional measure of work of breathing. Theoretical limitations of this measure as an index of the effort expended on breathing work include both the fact that the respiratory rate is not included and, if no air moves, no work is done despite the effort expended. The work of breathing in children with croup in this study is greater than that which has previously been documented in children with bronchiolitis (298), or bronchiolitis and bronchopneumonia (297). The rate of work of breathing (the product of the work of breathing and the respiratory rate) does compensate for the increase in respiratory rate, but in this study did not discriminate more effectively between normal and patients with croup.

The Pressure-Time Integral has been developed as an alternative measure of the effort of breathing, and has been shown to relate well to the rate of oxygen

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consumption (266,267,339). The Pressure-Time Integral in patients with croup was approximately five times that of controls, while the Work of Breathing and Rate of Work of Breathing were just over three times that of controls. The Pressure-Rate Product has previously been used to assess the effort of breathing of patients with severe oropharyngeal obstruction (269). It is easier to measure than the Pressure-Time Integral, as no flow trace (and in this context, no facemask) is required to delineate the timing of breathing, and appears to differentiate between patients with croup and normal children at least as well as the Pressure-Time Integral. The PRP in severe croup was more than double that recorded in children with life-threatening sleep-associated upper airway obstruction (269). Oesophageal pressure changes, and the derived measures of PRP and PTint, returned to the normal range following intubation of patients with severe croup.

The variable of Volume for Effort describes the amount of ventilation achieved in response to a particular respiratory effort and theoretically might be a more sensitive measure of croup severity. In fact, the Pressure-Rate Product highlights the difference between croup and control subjects much more effectively, and has the additional advantage that measurements of airflow are not required.

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6.2.3 Gas exchange

We did not measure arterial or end-tidal carbon dioxide tensions in our patients but were able to show that minute ventilation was not significantly decreased despite severe upper airway obstruction. It is probable that alveolar ventilation was decreased and dead-space increased in patients with severe croup as the respiratory rate was higher together with a lower tidal volume. This may explain the raised carbon dioxide tensions observed by others in severe croup (107,112,138,146).

Although no patients had an oxygen saturation of less than 92% while in room air throughout these studies, low arterial oxygen tensions in room air have been previously described (107) as a very common feature in croup and oxygen supplementation was required in a number of studies (137,138). In acute upper airway obstruction studies simulating croup (139), Rhesus monkeys decreased their arterial oxygen saturations significantly from baseline when inspiratory resistance

was increased to 1000 cm H_2O/L/s. The desaturation was quickly reversed by relieving the inspiratory resistance. The high effort of breathing with associated high consumption of oxygen may contribute to this hypoxemia. Small airways disease has also been implicated in the hypoxemia of croup because it has been shown in children dying of croup that mucosal inflammation extends throughout the respiratory tract and into more peripheral airways (63,340). Nonetheless, small airways disease cannot be inferred either from the study of healthy monkeys (139), the expiratory airway resistance measurements in intubated children with croup from measles (328) or from this study.

6.3 Conclusions

We have demonstrated that patients with severe croup maintain their minute ventilation by means of huge increases in intrathoracic pressure changes.

We have documented the presence of inspiratory flow limitation but not prolongation of inspiratory time in severe croup, and shown that expiratory glottic control may contribute to airway obstruction in this disease. Intubation, which bypasses the glottic area, reverses most of the pulmonary function changes although some variables did not return to normal, e.g. respiratory system compliance. Similarly, bypassing the upper airway obstruction did not unmask lower (small) airways obstruction, suggested to be present in post-mortem studies of children dying from croup.

It is clear from our data that measures of respiratory function which do not include intrathoracic pressure change are unlikely to be effective measures of the severity of croup in future studies. A number of easily measured parameters have been shown to separate croup and normal controls effectively. The Pressure-Rate Product may be the easiest to apply in the clinical situation, because of the relative ease with which it may be assessed over long periods, utilizing an oesophageal balloon catheter the size of a nasogastric feeding tube. Tidal flow-volume loop analysis may also be useful, particularly as it is relatively non-invasive, but suffers substantially from the need for

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sedation in order to apply a facemask to a distressed child in such a manner as to obtain a leak-free seal and reproducible recordings.

Chapter 7
The Effects of Adrenaline nebulisation

7.1 Introduction

Since benefits from the use of racemic adrenaline in post-intubation stridor were first reported in 1970 (219), several clinical studies with both adrenaline and racemic adrenaline nebulization in croup have demonstrated clinical improvement (111,115-117,126,154,220,221). A pure alpha-agonist, phenylephrine, has also been used to treat patients with croup effectively (141). However, clinical assessment of the degree of upper airway obstruction in this disease entity has proven to be faulty in inexperienced hands. Several clinical scores have been proposed, but none have been validated against outcome or accurate, objective and reproducible measures. Indeed, the difficulty of safely applying instrumentation to such acutely ill, small children has been an obvious hindrance to developing objective assessment criteria in this disease, and subsequent continuous monitoring devices.

In two clinical series, improvement in thoraco-abdominal phase angle asynchrony and tidal volumes (125) and tracheal antero-posterior diameter (145) were noted and in a case report on one 8-year old boy flow-volume loops showed improvement (9) following adrenaline nebulization. Although these techniques documented an objective response to adrenaline nebulization, none are direct measures of airway obstruction or the effort expended in overcoming it. Oscillometric measurement of pulmonary resistance in 8 infants in a convalescent phase of croup revealed a significant (30%) but temporary drop in total respiratory resistance in 7 of the 8 patients following administration of phenylephrine (141).

Studies of blood gases in patients with croup following adrenaline nebulization have shown improvement in transcutaneous CO_2 tension (137) and no change in oxygen saturation (128) Nonetheless, previous studies have demonstrated that blood gas analysis is not a useful tool for the clinical assessment of upper airway obstruction (107,135).

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Table 7.1: Response to nebulization – all patients (n = 17)

Variable	Before Adrenaline	After Adrenaline	Delta (Δ)	Paired t-test
	Mean (SD)	Mean (SD)	%	p value
Respiratory rate data				
Respiratory rate (b/min)	38.3 (7.2)	37.5 (8.54)	-2.1	0.61
I:E ratio	0.84 (0.09)	0.85 (0.13)	1.2	0.89
Inspiratory time (s)	0.74 (0.14)	0.76 (0.17)	2.7	0.32
Expiratory time (s)	0.88 (0.15)	0.91 (0.22)	3.4	0.33
Flow and volume data				
Peak inspiratory flow (ml/s)	98 (26)	104 (29)	5.7	0.25
Mid inspiratory flow (ml/s)	92 (25)	98 (27)	6.5	0.23
Peak expiratory flow (ml/s)	92 (30)	94 (22)	2.2	0.78
Mid expiratory flow (ml/s)	83 (31)	86 (22)	3.6	0.74
Tidal Volume (ml/kg)	**5.5 (1.0)**	**6.1 (1.7)**	**10.9 ***	**0.04 ***
Minute Ventilation (ml/min/kg)	223 (83)	235 (71)	5.4	0.25
Pressure data				
ΔPoes (cm H_2O)	**72 (29)**	**53 (28)**	**-26.4**	**0.01**
Indices derived from Flow-volume data				
AFV (ml/s.ml/kg)	**909 (385)**	**1072 (459)**	**17.9**	**0.07**
Tmif / Titot (%)	62 (12)	58 (12)	-6.5	0.19
Tmef / Tetot (%)	68 (16)	68 (20)	0	0.96
Mid-inspiratory flow / mid-expiratory flow	1.15 (0.2)	1.17 (0.17)	1.7	0.88
Indices derived from Flow-pressure data				
$R_{AW}0.5_I$ (cm H_2O/ml/s)	**431 (189)**	**320 (187)**	**-25.8**	**0.05**
$R_{AW}0.5_E$ (cm H_2O/ml/s)	**237 (108)**	**158 (66)**	**-33.3**	**0.004**
C_L (ml/cm H_2O/kg)	0.12 (0.19)	0.16 (0.31)	33.3	0.40
Indices of effort				
Pressure-Rate Product (cm H_2O.min)	**2116 (877)**	**1749 (929)**	**-17.3**	**0.046**
Pressure-Time integral (cm H_2O.s/min)	**1321 (489)**	**993 (459)**	**-24.8**	**0.0004**
Work of Breathing (gm.cm/kg)	**271 (134)**	**227 (122)**	**-16.2**	**0.02**
Rate of Work of Breathing (gm.cm/min/kg)	9646 (5574)	8154 (3997)	-15.5	0.1
Volume for Effort (ml/cm H_2O/s)	**1.89 (1.21)**	**2.75 (1.65)**	**45.5**	**0.0003**

* Statistically significant changes are highlighted in bold

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In this study we assessed the response of patients with severe croup to nebulization with adrenaline, using objective measures of the mechanics of breathing. Our hypothesis was that previously well-described measures of breathing mechanics, particularly those involving combinations of flow and pressure data such as Pressure-Rate product, would provide clear, objective evidence of responsiveness to therapy and may lend themselves to long term (i.e. continuous) monitoring methods.

The methods are fully described in Chapter 4.

7.2 Results

7.2.1 General

Eighteen patients were entered into the study, but acceptable data before and after adrenaline nebulization could only be collected from 17. The baseline results and the responses to adrenaline inhalation for all patients are shown in Table 7.1.

7.2.2 Pre and post adrenaline nebulization

Overall, for the 17 patients, there were no significant changes in respiratory rate, I:E ratio or flow measurements (Table 7.1). Flow measurements increased only slightly and not significantly. Tidal volume and minute ventilation increased by 11% ($p < 0.04$) and 5% (p = NS), respectively. ΔPoes dropped by 26% and the related measures of $R_{AW}0.5_I$, $R_{AW}0.5_E$, PRP, PTInt and Work of Breathing all decreased significantly. Volume for Effort increased by 45.5% ($p = 0.0003$).

Five of the 17 patients showed no change in mid-inspiratory airway resistance and PTInt following adrenaline nebulization. The group of non-responders was not different to the responders in terms of age, severity of disease or final outcome of the condition.

Three of the 5 non-responders were subsequently intubated on clinical grounds, while 5 of the 12 responders were intubated ($p = 0.47$, Fisher Exact Test).

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7.2.3 Adrenaline nebulization responders

Twelve of the 17 patients, aged 3.6 – 15.2 months (median 9.2 months) and weighing 6.5 – 14 kg (median 9.3 kg) showed a drop of > 10% in airway resistance and pressure-time integral following adrenaline nebulization. All flow measurements increased between 11% and 14% in this group. These patients were defined arbitrarily as responders (Table 7.2).

No cardiac arrhythmias were noted and nor did any blanching of skin occur following adrenaline. There were significant increases in inspiratory flow (mid and peak), mid expiratory flow, tidal volume and minute ventilation. AFV increased by 33% ($p < 0.004$) following adrenaline and Tmif /Titot was significantly changed after adrenaline nebulization while Tmef /Tetot did not.

ΔPoes dropped by 34.8% following adrenaline inhalation ($p < 0.001$). The related indices showed similar changes with marked decreases in PRP, Ptint, VFE and WOB but not Rate of WOB following adrenaline.

Mid-inspiratory and mid-expiratory airways resistances dropped significantly by 42% ($p = 0.004$) and 39% ($p = 0.003$) respectively following adrenaline.

Changes to individual traces following adrenaline nebulisation are shown in figures 7.1 and 7.2.

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7.2.4 Adrenaline versus saline nebulization

It was possible to perform studies before and after both saline and adrenaline nebulization on 6 patients aged 6.5 – 15.2 months (median 13.5 months) and weighing 7.9 to 12 kg (median 10.3 kg). All of these patients met the arbitrary criteria of responders to adrenaline. The only significant response to normal saline inhalation was for Pressure-Rate product which increased i.e. worsened ($p<0.001$). Neither adrenaline nor saline nebulization had any effect on pulse or respiratory rate, I:E ratio, blood pressure or oxygen saturation.

Table 7.2: Patients responding to adrenaline nebulization (n = 12)

Variable	Before Adrenaline	After Adrenaline	Delta (Δ)	Paired t-test
	Mean (SD)	**Mean (SD)**	**%**	**p-value**
Respiratory rate data				
Respiratory rate (b/min)	33.5 (5.2)	33.6 (6.99)	0.3	0.858
IE ratio	0.86 (0.09)	0.87 (0.13)	1.2	0.873
Inspiratory time (s)	0.80 (0.12)	0.81 (0.15)	1.3	0.638
Expiratory time (s)	0.927 (0.13)	0.95 (0.22)	2.5	0.61
Flow and volume data				
Peak inspiratory flow (ml/s)	**93 (21.3)**	**104 (31)**	**11.8 ***	**0.048 ***
Mid inspiratory flow (ml/s)	**87 (21.6)**	**99 (28)**	**13.8**	**0.037**
Peak expiratory flow (ml/s)	85 (21.4)	94 (23)	10.6	0.068
Mid expiratory flow (ml/s)	**76 (20.2)**	**86 (22)**	**13.2**	**0.047**
Tidal Volume (ml/kg)	**5.6 (1.0)**	**6.6 (1.7)**	**17.9**	**0.016**
Minute Ventilation (ml/min/kg)	**199 (45)**	**225 (48)**	**13.1**	**0.022**
Pressure data				
ΔPoes (cm H_2O)	66 (30)	43 (21)	**34.8**	**0.0014**
Indices derived from Flow-volume data				
AFV (ml/s.ml/kg)	**863 (331)**	**1149 (480)**	**33.1**	**0.0044**
Tmif / Titot (%)	**66 (9.9)**	**58 (10.2)**	**12.1**	**0.036**
Tmef / Te_{TOT} (%)	67 (19)	64 (22)	4.5	0.536
Mid-inspiratory flow / mid-expiratory flow	1.11 (0.18)	1.11 (0.21)	0.0	0.973
Indices derived from Flow-pressure data				
$R_{AW}0.5_I$ (cm H_2O/ml/s)	**441 (224)**	**257 (176)**	**41.7**	**0.004**
$R_{AW}0.5_E$ (cm H_2O/ml/s)	**228 (127)**	**139 (69)**	**39**	**0.003**
C_L (ml/cm H_2O/kg)	2.55 (3.71)	2.31 (3.3)	9.4	0.87
Indices of effort				
Pressure Rate Product (cm H_2O/min)	**1821 (792)**	**1269 (496)**	**30.3**	**0.016**
Pressure time integral (cm H_2O.s/min)	**1176 (474)**	**797 (296)**	**32.2**	**0.003**
Work of breathing (gm.cm/kg)	**258 (131)**	**203 (104)**	**21.3**	**0.001**
Rate of work of breathing (gm.cm/min/kg)	8146 (5036)	6727 (2829)	17.4	0.198
Volume for Effort (ml/cm H_2O/s)	**2.08 (1.4)**	**3.25 (1.7)**	**56.3**	**0.0001**

*** Statistically significant changes are highlighted in bold**

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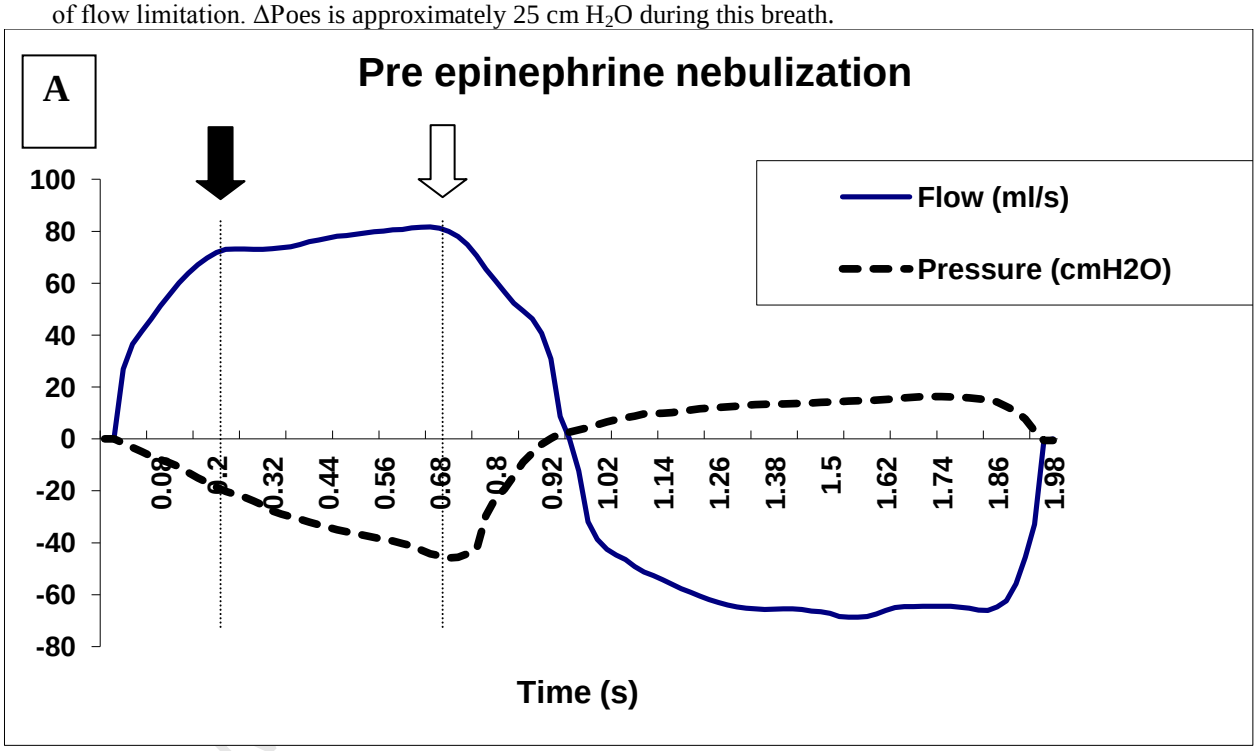
Figure 7.1: Patient with croup - Flow and Pressure Curves plotted against Time before and after inhaled adrenaline

A. Before adrenaline: Traces demonstrating inspiratory flow limitation. During initial inspiration there is a positive increase in inspiratory flow associated with a change in oesophageal pressure (left of solid arrow). To the right of the solid arrow, until inspiratory effort decreases (open arrow), there is virtually no further increase in inspiratory flow despite a large increase in negative pressure. During expiration, there is also evidence of flow limitation with oesophageal pressure higher and flows less than those seen in the patient after adrenaline inhalation (see Fig. 7.1B). ΔPoes is approximately 60 cm H_2O during this breath.

B. After adrenaline: From the beginning of inspiration, flow increases markedly up to the point marked by the solid arrow as pressure decreases. Thereafter, there is a further small decline in oesophageal pressure to its minimum but modest negative value (open arrow). During expiration, very modest increases in pressure are associated with relatively high flows. There is no evidence of flow limitation. ΔPoes is approximately 25 cm H_2O during this breath.



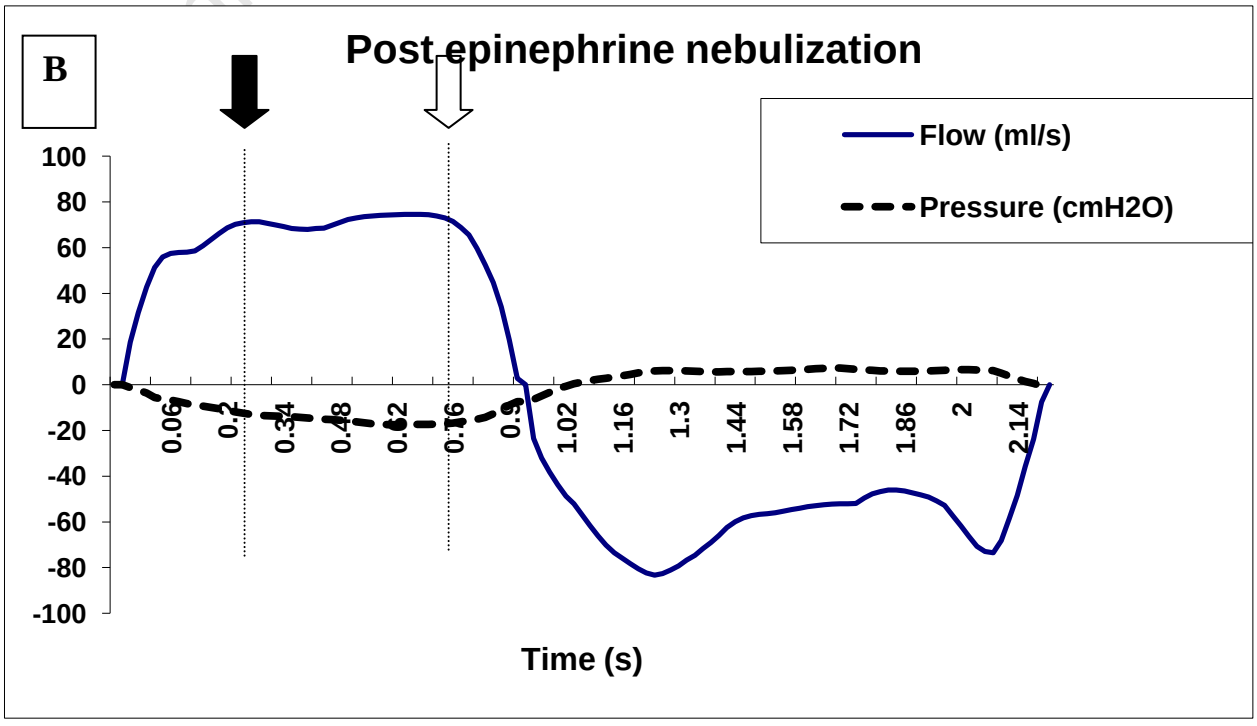


Figure 7.2: Patient with croup – Flow plotted against Pressure before and after inhaled adrenaline

A. Before adrenaline: In the upper left quadrant (inspiration) **t**here is considerable negative pressure (up to nearly -50 cm H_2O) generated to obtain flows of just over 75 ml/s. Despite increasing negative pressure, flow remains virtually unchanged from approximately –20 to –48 cm H_2O (open arrows). This demonstrates severe flow limitation during inspiration. In the lower right quadrant (exhalation), positive pressure of approximately 18 cm H_2O is generated to obtain flows of 70 $ml.s^{-1}$. There is no change in exhaled flow between approximately 10 and 18 cm H_2O. This demonstrates flow limitation during expiration.

B. After adrenaline: The negative pressures generated for both inhalation (upper left quadrant) and exhalation (lower right quadrant) are much less than before nebulized adrenaline was administered (-13 vs – 48 cm H_2O, inspiration; +12 vs + 18 cm H_2O, exhalation). There is no evidence of flow limitation during either inspiration or expiration.

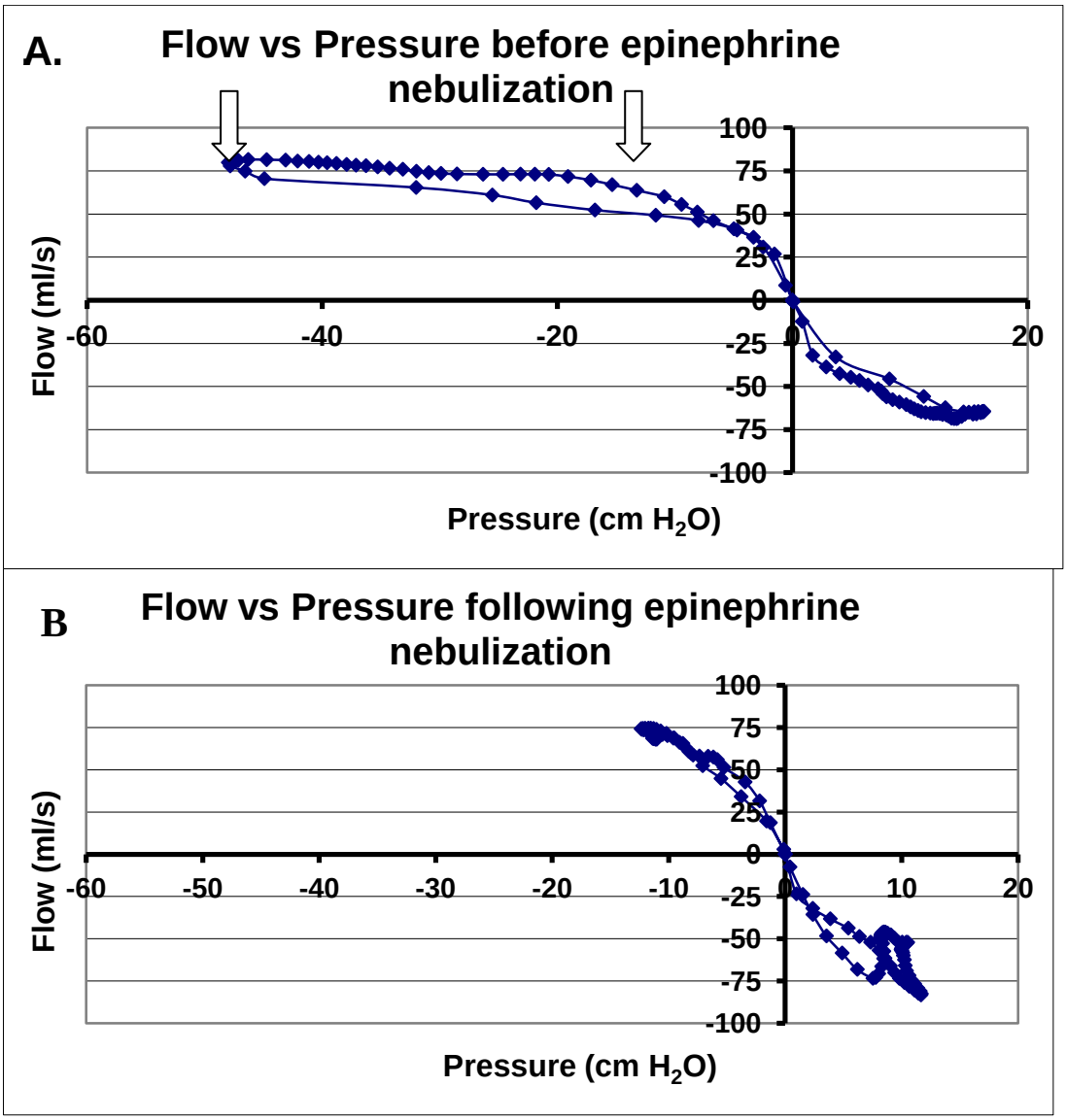
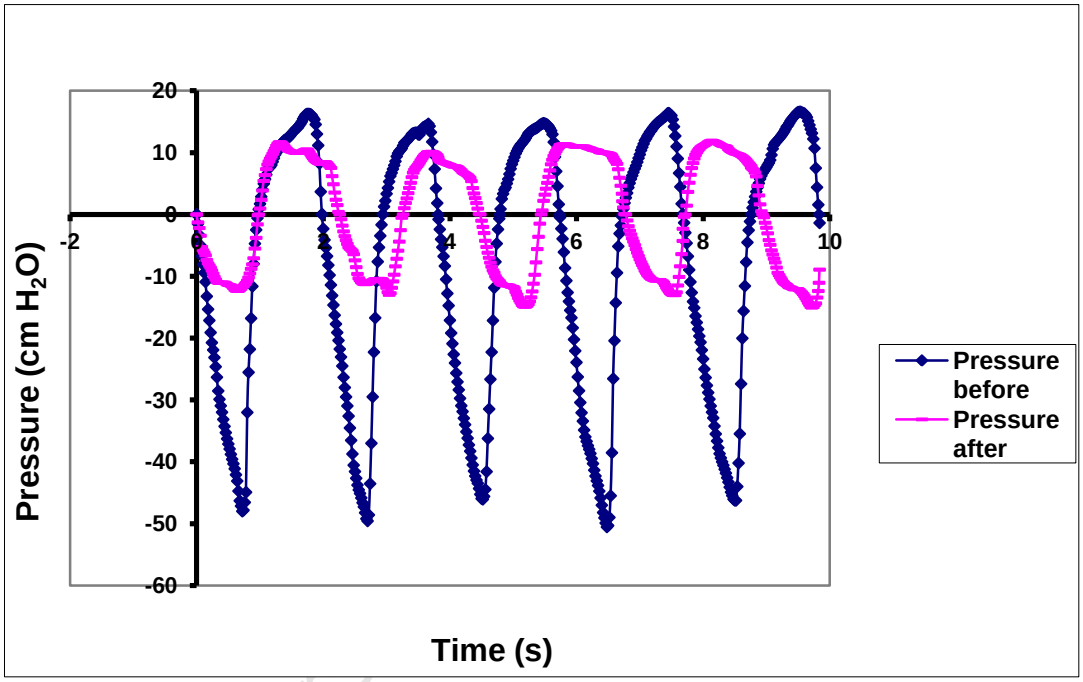


Figure 7.3: Patient with croup – Pressure traces plotted against Time before and after inhaled adrenaline

Prior to adrenaline inhalation, the pressure trace (blue line) shows negative pressure swings up to –50 cm H_2O during inhalation and positive pressure swings to about +18 cm H_2O during exhalation. Following adrenaline inhalation, the post-adrenaline trace (pink line) shows considerably less negative and positive swings (-12 and +10 cm H_2O for inhalation and exhalation, respectively), indicating that less effort is needed for respiration. Note the respiratory cycle is only slightly slower after adrenaline inhalation than before.



7.2.5 Responses to adrenaline over time

Data for 7 patients from before to 10 minutes following nebulization with adrenaline is shown in Table 7.4. Again, respiratory rate and I:E ratio did not change significantly over the period. Flow and tidal volume data showed initial increases, but had returned to baseline levels by 10 minutes post nebulization. Flow-volume indices did not change over this time. Pressure changes dropped markedly and this drop was sustained for at least 10 minutes at approximately 60% of baseline levels. Resistances (inspiratory and expiratory) decreased to 50% of baseline levels while PRP and PTint dropped to 40% and 60% of baseline levels respectively. Although changes in the work of breathing were not significant, the rate of work of breathing did drop significantly by 37%. VFE initially showed a 100% increase, which dropped to a 63% improvement over baseline by 10 minutes following nebulization.

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Table 7.3: Responses to adrenaline over time (n = 7)

Variable	Immediately before adrenaline	Immediately after adrenaline "0" minutes	5 minutes	10 minutes	One-way ANOVA compared to baseline
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value
Respiratory rate data					
Respiratory rate (b/min)	35.2 (7.3)	31.1 (5.6)	29.4 (4.1)	29.2 (4.9)	0.19
IE ratio	0.86 (0.10)	0.82 (0.07)	0.78 (0.11)	0.80 (0.07)	0.38
Inspiratory time (s)	0.81 (0.15)	0.89 (0.14)	0.90 (0.14)	0.93 (0.13)	0.46
Expiratory time (s)	0.95 (0.17)	1.09 (0.18)	1.17 (0.16)	1.17 (0.19)	0.09
Flow and volume data					
Peak inspiratory flow (ml/s)	101 (20)	117 (25)	113 (17)	107 (18)	0.46
Mid inspiratory flow (ml/s)	96 (21)	110 (23)	109 (16)	99 (16)	0.43
Peak expiratory flow (ml/s)	97 (18)	99 (18)	91 (14)	91 (14)	0.68
Mid expiratory flow (ml/s)	85 (19)	89 (19)	77 (16)	82 (13)	0.59
Tidal Volume (ml/kg)	6.0 (0.9)	7.6 (1.2)	7.3 (1.2)	7.5 (1.5)	0.10
Minute Ventilation (ml/min/kg)	213 (52)	235 (43)	213 (32)	214 (38)	0.70
Pressure data					
ΔPoes (cm H_2O)	69 (21)	**42 (11)***	**36 (10)***	**32 (9)***	**0.0001**
Indices derived from Flow-volume data					
AFV (ml/s.ml/kg)	1025 (316)	1401 (403)	1256 (374)	1254 (419)	0.34
Tmif / Titot (%)	66 (13)	58 (8)	60 (6)	69 (12)	0.18
Tmef / Te_{TOT} (%)	74 (17)	70 (22)	79 (17)	70 (19)	0.75
Indices derived from Flow-pressure data					
$R_{AW}0.5_I$ (cm H_2O/ml/s)	502 (205)	**218 (82)***	**222 (77)***	**242 (75)***	**0.0004**
$R_{AW}0.5_E$ (cm H_2O/ml/s)	244 (79)	**134 (46)***	169 (79)	157 (45)	**0.02**
C_L (ml/cm H_2O/kg)	3.5 (4.8)	3.1 (4.2)	7.2 (14.5)	1.6 (0.8)	0.60
Indices of effort					
Pressure-Rate Product (cm H_2O.min)	2188 (543)	**1286 (333)***	**1061 (403)***	909 (325)	**<0.0001**
Pressure-Time integral (cm H_2O.s/min)	1445 (329)	**836 (241)***	**847 (174)***	**863 (253)***	**0.0002**
Work of Breathing (gm.cm/kg)	339 (99)	253 (98)	237 (49)	250 (87)	0.13
Rate of Work of Breathing (gm.cm/min/kg)	11668 (3221)	**7685 (2689)***	**6845 (1135)***	**7310 (2885)***	**0.007**
Volume for Effort (ml/cm H_2O/s)	1.6 (0.76)	**3.0 (1.1)***	**2.6 (0.80)**	**2.6 (0.8)**	**0.035**

* indicates that the change from the baseline is significant < 0.05 level.

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7.3 Discussion

We have evaluated objectively the response of a group of patients with acute, severe croup to nebulization with adrenaline. The response to adrenaline nebulization was variable and 5 patients showed no response as defined by a <10% change in mid-inspiratory airways resistance or Pressure-Time integral, while 12 showed marked improvement by these criteria.

The variability of response to inhaled adrenaline by objective pulmonary function criteria presumably reflects the variability noted clinically by earlier investigators (125,141,145). Possible reasons for the lack of response in some patients include poor delivery of adrenaline to the laryngeal region, inadequate amounts of inhaled drug (we used a conservative dose of adrenaline according to some authorities), severity of disease, lack of available receptors for adrenaline or an adverse reaction to other constituents of the nebulization. The adrenaline solution used in this study is preserved with sodium metabisulfite and this could produce sulphur dioxide in the nebulized vapour (341). The failure to respond could then be related to a reaction to sulphur dioxide. Evidence against this is that a similar pattern of non-response was seen with racemic adrenaline (125), which is not preserved with sodium metabisulfite.

Responders to adrenaline nebulization showed increases in inspiratory and expiratory flow, tidal volume and minute ventilation immediately following nebulization. The improvement in response to adrenaline as measured by flow and volume changes is small, in the range of 10-20%. These benefits were not maintained and 10 minutes following nebulization these parameters were no different from baseline. By contrast, the marked changes in oesophageal pressures and pressure-related measures were sustained for at least the period of 10 minutes we were able to obtain measurements. These improvements in pressure-related measures ($R_{AW}0.5_I$, $R_{AW}0.5_E$, PRP, PTint) were in the range of 30 to 42%. The one tidal flow-volume parameter that appeared to show changes of a similar magnitude was the AFV (approximately 33%).

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It is possible that the increases in flow immediately after adrenaline, despite marked drops in the effort of breathing, are a reflection of the stimulatory effect of β-adrenergic agents on respiration, as earlier documented in non-human primates by Newth et al (225). We were not able to continue these recordings long enough to document the duration of changes in response to adrenaline, but these are expected to be relatively short-lived in view of the duration of action of adrenaline (approximately 20 minutes), and in keeping with published clinical data relating to adrenaline nebulization in croup (115-117).

We have previously demonstrated in Chapter 6 that inspiratory flow limitation is a feature of croup (Figures 7.1 and 7.2). Tidal airflow, tidal volume and minute ventilation are maintained in the normal range, even in severe croup, while the effort of breathing is markedly increased. This suggested to us that measurements of oesophageal pressure changes were essential to assess objectively the severity of airways obstruction in croup. That study also showed that tidal flow-volume analyses such as AFV and $Tmef/Te_{TOT}$ were clearly different between croup and controls and had the potential advantage of being relatively non-invasive measures of severity of disease. However, although air flow can be measured by facemask and pneumotachograph without any invasive procedures, our experience has been that small children with respiratory distress will tolerate facemasks only if sedated. This means that measurement of the AFV is not as non-invasive as it first appears. The pressure-related measurements are more invasive because they require an oesophageal catheter. The oesophageal catheter used in these studies was simply a nasogastric feeding tube which is a common accessory in intensive care, is well tolerated and no sedation is required while obtaining continuous measurements.

The present study has confirmed that changes in air flow and tidal volume are relatively insensitive measures of changes in respiratory mechanics in croup. $Tmef/Te_{TOT}$ did not demonstrate any change following adrenaline nebulization despite significant changes in the effort related to breathing. The area within the tidal flow-volume loop was, however, able to delineate differences in severity of upper airway obstruction in patients following adrenaline nebulization. This measure has not been reported in croup before although the area under the maximum expiratory

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flow-volume curve has been shown to be a sensitive marker of lung function impairment in adults (293,342).

There was no difference in the ability of PRP and PTint to detect changes in lung function following adrenaline nebulization. However, calculation of PTint requires a measure of flow to identify the beginning and end of inspiration and expiration, while PRP can be calculated from the trace of pressure change with each breath plotted against time, using a water-filled oesophageal catheter attached to monitoring equipment of the kind that is available in all intensive care units. Thus, PRP is a measure of severity of croup which can be readily used in the clinical setting for continuous assessment of responses to treatment.

Our data showed that the measurement of Work of Breathing itself did not appear to be useful in documenting changes in respiratory effort in this condition. Theory supports our findings in that WOB includes both recordings of pressure changes and flows. Therefore, if airflow is obstructed, the calculated work is decreased despite actual high effort. In addition, work does not include the respiratory rate whereas the rate of work of breathing does. Nonetheless, we did not find more pronounced changes in the Rate of Work of Breathing (17.4%) than by WOB alone (21%), because respiratory rate does not change after adrenaline inhalation, although flows and tidal volumes do. The same argument applies to the simple measurement of Poes (Δpeak-to-trough oesophageal pressure changes) alone, which provides as much significant per cent and statistical changes (26%, $p < 0.02$) as either PRP (17%, $p < 0.05$) or PTInt (25%, $p < 0.05$), both of which include respiratory rate. This is demonstrated in Figure 7.3 and Table 7.3.

The parameter, Volume for Effort, is affected by both changes in effort and minute ventilation. In this study we have shown that this parameter clearly shows significant changes in response to adrenaline nebulization. However, it too requires a facemask application for flow measurements, with its associated drawbacks.

The current investigation was never intended as a therapeutic trial or outcome study. The numbers of patients from the responders versus the non-responders groups who

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required intubation were statistically similar. The decision to intubate was made clinically by paediatricians experienced in the management of viral croup.

We conclude that most (but not all) patients with acute severe croup respond to nebulization of adrenaline with a clinically significant but temporary improvement in respiratory mechanics as assessed by respiratory resistance, changes in oesophageal pressure and PRP, Pressure-Time integral and Volume for Effort. Analysis of flow-volume loops was not able to detect these improvements with the exception of the area within the flow-volume loop. The insertion of a (minimally invasive) feeding tube provided both the oesophageal pressure change with respiration and the Pressure-Rate product. These are simple, continuous measures which were as accurate as any other measurements in determining the response to inhaled adrenaline and were well tolerated. Either of these measurements and their change over time, continually displayed as a number or waveforms on a bedside monitor, should be investigated as a severity assessment tool for upper airway obstruction in croup. Objective criteria for determining either improvement or need for intubation will complement clinical assessment which has sometimes proven faulty.

In addition, the short time of response to adrenaline noted by us, and others (116,126,154) previously, suggests either higher doses of nebulized adrenaline and the associated dose-responses should be investigated or the response to continuous inhalations (probably delivered by nasal catheter rather than face mask) of low concentrations of the drug should be evaluated.

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Chapter 8
Clinical Signs of Airway obstruction in Acute Severe Croup

8.1 Introduction

Clinical assessment of disease severity may be subjective. While this may not be problematic when a single observer is following the clinical course of an individual patient, it may cause significant problems when a number of observers are required to manage patients over a period of time. One response to this difficulty has been the development of scoring systems of disease severity. Clinical scores have been developed in a wide range of conditions, and within the range of respiratory disease for children scores have been developed and utilized for lower respiratory tract infections, asthma (343-346) bronchiolitis (239,239,347,348) , for the prediction of hypoxaemia in bronchiolitis and pneumonia (349) and for the assessment of croup.

Clinical scores of illness severity are used in a number of ways: to assess the severity of the disease for research purposes (this may be used to assess response to therapy or to assess the overall outcome of patient management in a particularly area or institution); to predict possible outcome; and finally as a basis for decision making. Ideal scoring systems would be highly reproducible when used by a range of observers over a period of time, and simple enough for reliable use by relatively inexperienced personnel. In addition the ideal clinical score should be validated: against an objective measurement of severity of disease; against outcome; over a range of severity of illness; against its predictive value for predicting appropriate intervention and for interobserver error (109) and reproducibility.

A number of clinical scoring systems have been published and used as tools for the assessment of severity of croup in clinical trials (Table 2.5). There is wide variation both in clinical features assessed and the method of scoring of each feature.

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This study set out to review the scoring systems for evaluation of severity of croup, to critically evaluate the parameters and processes utilized in those studies, and to compare these parameters with objective data on patients with acute severe croup.

8.2 Theoretical aspects of croup severity assessment

Croup is a condition characterized clinically by stridulous breathing; pathologically by inflammation and oedema of the subglottis (although other parts of the respiratory tract may also be involved); aetiologically by viral infections excluding measles and herpes.

Assessment of severity of illness could reasonably be directed at the assessment of severity of airways obstruction. However, it is possible for lung consolidation to be part of the clinical picture, and it is therefore not adequate simply to assess the severity of airways obstruction. Likewise, children with viral infections may have complicating features such as pyrexia and gastrointestinal disease which may also add to the complexity of assessment of severity of illness. However the data of lung function following endotracheal intubation in severe croup (see chapter 6) does suggest that in the majority of patients the core problem is that of severe airway obstruction at the level of the larynx, and thus reproducible evaluation of severity of airways obstruction is probably the most critical component of severity assessment.

As the severity of airway obstruction increases one would expect that the majority of patients would respond by increasing the effort of breathing in an attempt to overcome the resistance and maintain normal gas exchange. Ventilation would be maintained until a point where the effort required to overcome that resistance is higher than the child can sustain.

One would therefore predict that there would be a phase of respiratory compensation, followed by a phase of respiratory decompensation. This prediction appears to be correct for conditions such as asthma where pulsus paradoxus has not been a reliable clinical sign of severe asthma. The objective measures of respiratory

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mechanics, physical signs and their significance may well differ during the two phases.

In order for clinical parameters in scoring systems to be acceptable, they need to meet the following criteria:

Clear definition of the parameter

Clear definition of the score to be attached to that parameter

Reproducibility between observers and well as for the same observer on repeated occasions

Appropriate linkage to the condition that is being scored.

8.3 Review of Croup Scoring systems

Scoring systems for croup were identified by searching Medline using the Mesh terms croup and outcome assessment. Any studies identified as showing clinical outcome from any intervention were reviewed for the use of a clinical scoring system. Any scoring systems identified were traced back to the original report where possible.

8.4 Results of searches

All croup clinical scoring systems identified in the search were noted in table 2.5 (see chapter 2). A total of 19 scoring systems were identified. Three of these systems were modifications of the "Westley Score" (115) and one other was a modification of the score originally reported by Westley et al (116).

Once croup scores had been identified, the criteria utilized in those scores, and the way in which those criteria were graded were shown in table 2. As can be seen there are a wide range of criteria used, and a wide range of scores attached to those criteria. Very few of those criteria are defined in unambiguous terms.

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Table 8.1: Criteria used in clinical scoring systems

Criteria	Scoring system	Scores or grade allocation
Ross (110)		
Croupy cough	Present	
Suprasternal and supraclavicular retraction	Absent or present,	
Sternal retraction	Present or absent	
Stridor	Present or absent	
Cyanosis	Present	
		Scored as mild when only croup cough with suprasternal and supraclavicular retractions. Moderate when above together with "marked stridor" and sterna retractions. Severe when "extreme retractions and early cyanosis"
Gardner et al (111)		
Croup cough	not present, present only when agitated present at rest	0 1 2
Anxiety/air hunger	not present, present only when agitated present at rest	0 1 2
Stridor	not present, present only when agitated present at rest	0 1 2
Retractions	not present	0

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Criteria	**Scoring system**	**Scores or grade allocation**
	present only when agitated present at rest	1 2
Cyanosis	not present present only when agitated present at rest	0 1 2
	Total Maximum score	**10**
Wesley (112)		
Stridor	Absent or present	
Intercostal and subcostal recession	Absent or present	
Breath sounds	normal or reduced on auscultation	
Cyanosis	Absent or present	
Signs of fatigue	muscular hypotonia or stupor	
		Graded as mild if had stridor and recession, severe if had stridor, recession, with restlessness and/or hypotonia and/or cyanosis. Moderate if anything in between
Downes and Rafaely (113)		
Inspiratory sounds	normal, harsh with ronchi, delayed	0 1 2
Stridor	none, inspiratory, inspiratory and expiratory	0 1 2
Cough	None Hoarse cry Bark	0 1 2
Retractions or flaring	none,	0

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Criteria	**Scoring system**	**Scores or grade allocation**
and intercostal retractions	flaring and suprasternal retractions, these plus subcostal	1 2
Cyanosis	none, in air, in 40% oxygen	0 1 2
	Total Maximum	**10**
Taussig et al (115)		
Color	normal, dusky, cyanotic in air, cyanotic in 30-40% oxygen	0 1 2 3
Air entry	normal, mildly diminished, moderately diminished and substantially diminished	0 1 2 3
Retractions (relative to level of consciousness)	none, mild, moderate, severe	0 1 2 3
Level of consciousness	normal, restlessness, lethargy (depression)	0 1 2
Stridor (Relative to state of rest or agitation)	none, mild, moderate, or no stridor in the presence of other signs of severe obstruction	0 1 2 3
	Maximum Total	**14**
Westley et al (116)		
Level of consciousness	Normal (including sleep) Disorientated,	0 5

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Criteria	**Scoring system**	**Scores or grade allocation**
Colour	normal, cyanotic in room air, cyanotic in oxygen	0 4 5
Stridor	none, when agitated, at rest, severe	0 1 2
Air entry	normal, decreased, markedly decreased	0 1 2
Retractions	none, mild, moderate, severe	0 1 2 3
	Total Maximum	**17**
Fogel et al (117) **– modified from Westley**		
Level of consciousness	Normal Restless Lethargic	0 2 4
Colour	Normal Cyanotic in room air Cyanotic in oxygen	0 2 4
Stridor	None When agitated At rest Severe	0 1 2 3
Air entry	Normal Decreased Markedly decreased	0 1 2
Retractions	None Mild Moderate Severe	0 1 2 3

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Criteria	**Scoring system**	**Scores or grade allocation**
	Total Maximum points	**16**
Syracuse Score (119)		
Stridor	None Audible on close examination or with a stethoscope Easily audible; patient unable to lie down comfortably	0 1 2
Cyanosis	None Minimal cyanosis of nailbeds and / perioral mucosa Obvious cyanosis	0 1 2
Sternal retraction	None Present	0 1
Respiratory rate	Specific ranges specified for different weight categories	0 -3
Pulse rate	Specific ranges specified for different weight categories	0 – 3
	Total Maximum	**11**
Klein (120)		
Inspiratory stridor	Present	Grade 1
Inspiratory and Expiratory stridor	Present	Grade 2
Inspiratory and Expiratory stridor with Pulsus paradoxus / active abdominal Expiration	Present	Grade 3
Extremis	Present	Grade 4
Kuusela and Vesikari (121)		
Stridor	No stridor or dyspnoea Mild stridor, Strong	0 1 2

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Criteria	**Scoring system**	**Scores or grade allocation**
	obvious dyspnoea	3
Cough	None Productive mild and strong barking	0 1 2 3
	Total Maximum	**6**
Super et al (122)		
Stridor	none, at rest with stethoscope, at rest without stethoscope	0 1 2
Retractions	none, mild, moderate, severe	0 1 2 3
Air entry	normal, decreased, severely decreased	0 1 2
Cyanosis	none, with agitation, at rest	0 4 5
Level of consciousness	normal, altered mental status	0 5
	Total maximum	**17**
Sivan et al (125)		
Stridor	only during agitation or crying, at rest but with no distress, with distress or chest retractions or nasal flaring	1 2 3
Cyanosis	present together with severe stridor (above)	4
Waisman et al (126)		
Modified the Downes and Rafaely score by substituting		

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Criteria	**Scoring system**	**Scores or grade allocation**
oxygen saturation <95% for cyanosis.		
Kristjanssen et al (128)		
Inspiratory stridor	None	0
	When agitated	1
	On /off at rest	2
	Continuous at rest	3
Retractions	None	0
	Mild	1
	Moderate	2
	Severe	3
Air entry	Normal	0
	Decreased	1
	Moderately decreased	2
	Severely decreased	3
Cyanosis	None	0
	When crying	2
	At rest	3
State of consciousness	Normal	0
	Restless or anxious	2
	Depressed	3
	Maximum Total	**15**
Geelhoed and Macdonald (130)		
Stridor	None	0
	Only on crying, exertion	1
	At rest	2
	Severe (biphasic)	3
Retractions	None	0
	Only on crying, exertion	1
	At rest	2
	Severe (biphasic)	3
	Maximum total	**6**

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Criteria	**Scoring system**	**Scores or grade allocation**
Luria et al (123) Used a modified Westley score		
Stridor	None Only with agitation or excitement At rest with stethoscope At rest without a stethoscope	0 1 2 3
Retractions	None Mild Moderate Severe	0 1 2 3
Air Entry	Normal Decreased Severely decreased	0 1 2
Cyanosis	None With agitation At Rest	0 4 5
Level of consciousness	Normal Altered mental status	0 5
	Total Maximum	**18**
Johnson et al (131,189)		
Barking cough	Occasional Frequent Not prominent	
Stridor	None to limited stridor at rest Easily audible at rest Prominent inspiratory and occasionally expiratory stridor Audible stridor at rest (occasionally hard to hear)	
Suprasternal and intercostal indrawing	None to mild At rest	

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Criteria	**Scoring system**	**Scores or grade allocation**
	Marked retractions Retractions (may not be marked)	
Distress or agitation	None Little to none Significant distress and agitation Lethargy or decreased level of consciousness	
Dusky complexion	No comment Often without oxygen supplementation	
		Overall graded as mild (without stridor or significant indrawing at rest), moderate (stridor and chest wall indrawing at rest without agitation) or severe (stridor and indrawing of the sternum associated with agitation or lethargy)
Husby et al (127) **Overall clinical assessment score (modification of Westley)**		
Inspiratory stridor	Assessed with and without help of stethoscope	0 – 4
Cough		0 – 3
Retractions	Assessed at 4 sites: jugulum, supraclavicular, intercostal and subcostal	0 – 3
Colour	Cyanosis in air Cyanosis after oxygen	2 4
Dyspnoea		0 – 3
	Total Maximum	**17**

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Criteria	**Scoring system**	**Scores or grade allocation**
Nutman (129) **(stridor scoring system and not used specifically on croup)**		
Level of consciousness	Normal (including sleep) Altered mental status (lethargy)	0 5
Cyanosis when breathing room air	None When agitated Cyanosis at rest	0 4 5
Inspiratory stridor	None When agitated At rest	0 1 2
Air movement	Normal Decreased Markedly decreased	0 1 2
Retractions	None Mild (alar flaring) Moderate (suprasternal and intercostal) Severe (all accessory muscles used)	0 1 2 3
	Total Maximum	**17**
Chan et al, (132)		
Stridor	None With Stimulation At rest Inspiration and expiration at rest	0 1 2 3
Retractions	None Mild Moderate Accessory muscles	0 1 2 3
Air Entry	Normal Mild decrease Moderate decrease	0 1 2

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Criteria	Scoring system	Scores or grade allocation
	Markedly decreased	3
Colour	Normal	0
	Cyanosis	3
Level of Consciousness	Normal	0
	Restless when disturbed	1
	Anxious or restless (undisturbed)	2
	Lethargic	3
Cough	None	0
	Harsh cry	1
	Bark	2
	Severe paroxysms	3
	Total Maximum	**18**

8.4.1 Components of Scoring systems

Data from Table 8.1 was reorganised to highlight the clinical signs that have been used for the assessment scores in croup, and to highlight the range of definitions given to those clinical signs. That data is shown in table 8.2.

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Table 8.2: Symptoms and signs used in clinical scoring systems

Symptom	**Studies in which this has been used**	**Criteria**
Croup cough	Ross (110) Gardner et al (111), Kuusela and Vesikari (121), Downes and Rafaely (113), Waisman et al (126), Johnson et al (189), Husby et al (127), Chan et al (132)	Present or absent not present, present at rest, present only when agitated (111) productive, mild and strong barking (121) none, hoarse cry, bark (126)(113) Barking cough – occasional, frequent, not prominent (189) No specific guidelines (127) None, harsh cry, bark, severe paroxysms (132)
Air hunger or anxiety or dypsnoea	Gardner et al (111), Kuusela and Vesikari (121)	not present, present at rest, present only when agitated(111) absent or obvious (121) (Chan et al felt that this sign was incorporated into the category of level of consciousness (132))
Retractions	Ross (110) Gardner et al (111), Downes and Rafaely (113), Waisman et al (126), Taussig et al (115), Westley et al (116), Fogel et al (117) – modified from Westley, Super et al (122), Wesley (112), Syracuse Score (119), Kristjansson et al (128), Luria et al (123), Johnson et al (189), Husby et al (127), Chan et al, (132)	Mild, moderate or severe (110)(123) not present, present only when agitated (111), none, flaring and suprasternal retractions, these plus subcostal (113,126) mild, moderate or severe (relative to level of consciousness (115)) none, mild, moderate, severe (116)(117)(128)(122) Intercostal and subcostal recession absent or present

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Symptom	**Studies in which this has been used**	**Criteria**
		Sternal retraction – none or present (119) Suprasternal and intercostal indrawing – none to mild, at rest, marked retractions, retractions (may not be marked) (189) Assessed at jugulum, supraclavicular, intercostal and subcostal (127) None, mild, moderate and use of accessory muscles (132)
Cyanosis	Ross (110), Gardner et al (111), Wesley et al (112), Downes and Rafaely (113), Waisman et al (126), Taussig et al (115), Wesley et al, 1974, Westley et al (116) , Super et al (122), Sivan et al (125), (117) – modified from Westley, Syracuse Score (119), Kristjansson et al (128), Luria et al (123), Johnson et al, (189), Husby et al (127), Chan et al (132)	Present or absent (110,132) not present, present at rest or only when agitated (111)) none, in air, in 40% oxygen (Downes and Rafaely (113)) present or absent (112) colour normal, dusky, cyanotic in air, cyanotic in 30-40% oxygen (116)(115) none, with agitation, at rest (122) present (or absent) together with severe stridor (125) oxygen saturation of <95% in air or in 40% oxygen (126) normal, cyanotic in room air, cyanotic in oxygen (117) none, minimal cyanosis of nailbeds and / perioral mucosa, obvious cyanosis (119) none, when crying, at rest (128)

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Symptom	**Studies in which this has been used**	**Criteria**
		none, with agitation, at rest (123) dusky complexion – no comment, often without oxygen supplementation (189) cyanosis in air, cyanosis after oxygen (127)
Stridor	Gardner et al (111), Westley et al (116), Wesley et al 1974 (112), Downes and Rafaely (113), Waisman et al(126), Taussig et al (115), Westley et al, Klein (120), Kuusela and Vesikari (121), Super et al (122), Sivan et al(125), (117) – modified from Westley, Syracuse score (119), Kristjanssen et al (128), Geelhoed and Macdonald(130), Luria et al (123), Chan et al (132)	present or only when agitated (111) absent or present (112) none, inspiratory, inspiratory and expiratory (113,126) none, mild, moderate or no stridor in the presence of other signs of severe obstruction (relative to state of rest or agitation) (115) none, when agitated, at rest, severe (116), (117) inspiratory, expiratory and both (120) none, mild, strong and obvious dyspnoea (121) none, at rest with stethoscope and at rest without stethoscope (122) only during agitation or crying, at rest but with no distress, with distress or chest retractions or nasal flaring (125) None, audible on close examination or with a stethoscope, easily audible,

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Symptom	**Studies in which this has been used**	**Criteria**
		patient unable to lie down comfortably (119) None, when agitated, on / off at rest, continuous at rest (128) None, only on crying or exertion, at rest, severe (biphasic) (130) None, only with agitation or excitement, at rest with stethoscope, at rest without a stethoscope (123) None to limited stridor at rest, easily audible at rest, prominent inspiratory and occasionally expiratory stridor, audible stridor at rest (occasionally hard to hear) (189) None, with stimulation, at rest, inspiration and expiration at rest (132)
Breath sounds or air entry	Wesley et al (112), Downes and Rafaely (113), Waisman et al (126), Taussig et al (115), Westley et al (116), Super et al (122) (117) – modified from Westley, Kristjansson et al (128), Luria et al (123) Johnson et al (189), Chan et al (132)	normal or reduced on auscultation (112) normal, harsh with ronchi, delayed (specifically for inspiratory sounds) (113,126) normal, mildly diminished, moderately diminished and substantially diminished (115,132) normal decreased, markedly decreased (116)(117) normal, decreased, severely

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Symptom	**Studies in which this has been used**	**Criteria**
		decreased (122)(123) normal, decreased, moderately decreased, severely decreased (128)
Signs of fatigue	Wesley et al (112)	presence or absence of muscular hypotonia or stupor
Level of consciousness	Taussig et al (115), Westley et al (116), Super et al(122), Fogel et al (117) – modified from Westley, Kristjansson et al (128), Luria et al (123)	normal, restlessness, lethargy / depression (115) normal, disorientated (116) normal, altered mental status (122)(123) normal, restless, lethargic (117) normal, restless or anxious, depressed (128)
Distress or agitation	Johnson et al (189)	None, little to none, significant distress and agitation, lethargy or decreased level of consciousness (189)
Pulsus paradoxus	Klein(120)	present or absent (120)
Active abdominal expiration	Klein(120)	present or absent (120)
Respiratory rate	Syracuse Score (119)	Specific ranges specified for different weight categories (119)
Pulse rate	Syracuse Score (119)	Specific ranges specified for different weight categories (119)
Dyspnoea	Husby et al (127)	No specific guidelines given (127)

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8.4.1.1 Croup cough

The scoring systems that have used the presence of a cough have defined the related scores in a variety of ways (Table 8.3). Scores have related to both the presence or absence of a cough (also under a variety of conditions) or the nature of the cough.

8.4.1.2 Air Hunger / anxiety / dyspnoea

Both scores using this parameter (111,121) have scored on the basis of present or absent, but under different circumstances. It is likely that the presence of this clinical sign will be associated with severe airway obstruction. However the parameter is not clearly defined and the use of sedation may well hide this sign. An exhausted patient may not show obvious signs of air hunger.

8.4.1.3 Retractions

The presence of chest wall retraction is used by several of the scoring systems. Some scores have simply assessed whether any retraction was present, while others focussed on recession of different regions including sternal, suprasternal, supraclavicular, intercostals or subcostal. Recession of different regions of the chest wall may be related to a range of different pathophysiological processes. In some systems the retraction has been linked to the level of consciousness or to the presence of agitation.

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8.4.1.4 Cyanosis and oxygen saturation

As can be seen from the table the presence or absence of cyanosis is used in a number of scoring systems. One system even differentiated between nailbed and perioral cyanosis and "obvious cyanosis". Additional factors such as the ambient oxygen concentration and the presence of agitation are also considered.

8.4.1.5 Stridor

The presence or absence of stridor under different conditions of arousal is a common feature of many of the scoring systems. Several systems differentiated between

inspiratory and expiratory stridor, while others graded stridor on the basis of whether a stethoscope was required to detect the clinical sign.

8.4.1.6 Breath sounds or air entry

The nature of breath sounds or the assessment of air entry is used in a number of scoring systems, with a variety of criteria for allocating scores

8.4.1.7 Signs of fatigue

Wesley et al (112) refer to the presence or absence of signs of fatigue, but these signs are not defined.

8.4.1.8 Level of consciousness

Level of consciousness is used in a number of scoring systems (115,116,122). It is difficult to explain how level of consciousness should be related to the severity of airways obstruction unless the patients have become hypoxaemic. Kemper et al (109) showed that interobserver variability in assessment of level of consciousness is at best moderate. Chan et al, reported that of a cohort of 158 children with croup only 2 had a disturbance of level of consciousness (132). It is also likely that restlessness in small children may be associated with a number of factors other than the severity of croup, and may thus be a confusing factor.

8.4.1.9 Pulsus paradoxus

The scoring system of Klein (120) is the only score that utilizes the presence or absence of pulsus paradoxus.

8.4.1.10 Active abdominal expiration

The Klein score is the only score to use the parameter of active abdominal expiration.

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8.4.2 Validation of scoring systems

Only the scoring system of Sivan et al (125) has been compared with objective measurements of mechanics of breathing. In that study (of 5 patients with croup) objective measurements of air flow, tidal volumes, and thoraco-abdominal asynchrony were measured before and after the administration of epinephrine nebulization, and it was shown that there was correlation between the clinical scoring system and the objective measures of severity.

The Syracuse score has been validated against the outcome of patients assessed (108). It was found to be useful, in an outpatient setting, to predict which children could safely be admitted to a general paediatric ward in preference to an ICU (108). The score did not however accurately predict which children would require ICU admission. As the study looked at a population of 165 children of whom only 3 were intubated, and the mean and median scores were 5.7 and 5.5 respectively (out of a maximum score of 15) it did not assess the validity of the score for the assessment of more severe croup. The score is thus validated for use with regard to the question of route of admission, but not in terms of timing of intervention such as endotracheal intubation.

The score reported by Chan et al, has been evaluated in an outpatient setting (132). They used a score with a maximum score of 18, and found that the reliability of clinical signs was less than had been expected. Important differences between this study and some of the research studies, include the fact that the scores were done by a wide variety of clinical staff, and not simply a research team. This study really only evaluated patients in the mild spectrum of disease (with a mean score of 3.5 (out of possible 18).

The Klein score has been used to identify the need for intubation (unpublished data from experience at the Red Cross War Memorial Children's Hospital, Klein M), but not necessarily the need for hospital admission. The experience suggests that if children with persistent grade 3 croup are intubated, there is an extremely low rate of unexpected collapse among children with severe croup. It is however possible that some children were intubated who did not need this intervention.

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8.4.3 Structure of Scoring systems

The scoring systems function in different ways, some are purely linear scores with increments of 1 for each parameter, others such as the Westley score have introduced a grading in the implications of certain signs, so as an example: cyanosis automatically goes to score 5 (0 for no cyanosis). In others the presence of a particular parameter automatically assigns a specific grade, while certain parameters automatically increase the grade to the highest level.

There is a considerable range in the maximum number of points that can be allocated within the scoring systems, with a maximum of 18 points (123(123,132)) and as few as 4 in the Klein score. There is no data available regarding the discriminatory power of the scores and what change of score can be related to any clinical significance. However it is likely that the Klein score will group wide ranges of severity of illness, while other scores attempt to discriminate between many levels of severity.

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8.5 Discussion

This review has highlighted the wide range of scoring systems, the range of clinical criteria that have been included in the systems, the variety of scoring mechanism utilized and the lack of objective validation of these scores.

8.5.1 Clinical criteria

A striking feature is the range of clinical criteria that have been incorporated into clinical scoring systems. Many of these signs are poorly defined in the scoring systems (although the exact definitions may have been clear to the original authors of the scores).

On review of the more common clinical signs, it is of interest to compare the signs with the data that we have presented earlier in this thesis.

It is likely that chest wall retraction will be at least partially related to intrathoracic pressure changes, and as noted in both chapters 6 and chapter 7 intrathoracic pressure changes are clearly related to the severity of airway obstruction. The patients in our study did have severe croup, and it is possible that chest wall retraction is a clinical sign that is more relevant in patients with more severe disease, and less so in patients with milder airway obstruction. In addition the amount of retraction may be related to other factors including the thickness of the chest wall (including muscle bulk, subcutaneous tissue and age) and the level of patient fatigue, and it is not clear how reliable this sign is.

In the presence of cyanosis, there may be little doubt that a child is hypoxic, however in a study in Papua New Guinea, Wandi et al (350) showed that clinical signs are not effective at predicting hypoxaemia and children may become significantly hypoxic in the absence of cyanosis. It is thus appropriate to use pulse oximetry as used in the score of Waisman et al (126). Newth et al (107) have previously shown that hypoxaemia (as assessed by arterial blood gas analysis) is a common feature in patients with severe croup. Data in Chapters 6 and 7 shows that patients may have severe airways obstruction with no associated cyanosis or low oxygen saturations. It is clearly important that the oxygen concentration of inhaled gases be taken into account in assessment of hypoxaemia as a marker of severity of croup.

Only 4 systems (Klein (120), Downs and Rafaely (113), Chan et al (132) and the modification by Waisman (126)) have considered the presence of stridor during inspiration or expiration as a feature. The study of Kemper et al (109) in patients with post extubation stridor showed only moderate interobserver agreement for the presence or absence of stridor. In the study of Chan et al (132) stridor, with an agreement of 0.4 to 0.5 (using Cohen's quadratic weighted kappa) showed the highest agreement between observers of the clinical signs used.

The early study by Taussig et al (115) also put stridor in a context ("relative to state of rest or agitation") and made "no stridor in the presence of other signs of severe obstruction" an item that scored the same points as severe stridor.

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Although assessment of breath sounds or air entry has been shown to be unreliable by Kemper et al (109) this is a common feature of the scores. Breath sounds or air entry, are probably related in part to the rate of air flow or the tidal volumes during respiration. It seems unlikely that small changes in tidal volume and flow will be reliably assessed clinically. Data from our studies (chapter 6 and 7) has shown that there is a significant difference in some aspects of flow and tidal volume between croup and normal patients, but very little difference in flow and tidal volume between patients with varying severity of croup. However the patients in this study were at the severe end of the spectrum of airway obstruction, and the possibility remains that breath sounds may be useful clinical signs (and components of scoring systems) in milder patients, but not in more severe patients (where flow limitation is taking place).

The scoring system of Klein (120) is the only score that utilizes the presence or absence of pulsus paradoxus, or the presence or absence of active abdominal expiration. There is no data available on interobserver agreement on the assessment of a palpable pulsus paradoxus. However Steele et al demonstrated on a single adult volunteer that there was poor correlation between intra-arterial pressure assessment of pulsus paradoxus and manual measurement of pulsus paradoxus (118). In that pilot study they were able to non-invasively measure pulsus paradoxus using a finger arterial pressure monitor, and showed that the trace from a pulse oximeter had potential as a non-invasive assessment of pulsus paradoxus. Subsequently Frey and Butt (351) reported that in 62 unintubated children, 57 had photoplethysmographic traces from pulse oximeters that could be assessed, and the sensitivity and specificity of a photoplethysmographic fluctuation of 8mm to detect a pulsus paradoxus of > 10 mmHg were 89% and 90% respectively.

Steele et al (144) showed that there was good correlation between the size of the pulsus paradoxus and the Westley score for croup in a subset of patients with severe croup. In addition they demonstrated that adrenaline nebulisation was associated with a drop in Westley croup score of 1.5 and a drop in pulsus paradoxus of 7.5±11.8(s.d) mm Hg. This relationship was statistically significant.

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The presence and size of pulsus paradoxus in asthma has been used in a number of scores of asthma severity, although its use has fallen into disfavour. Martell et al (352) showed that there was no correlation in severe asthma between pulsus paradoxus and pCO_2 while the pCO_2 was < 35mmHg. However when the pCO_2 was > 35 there was a directly proportional correlation.

Galant et al (353) showed that there was no correlation between the pCO_2 and the size of the pulsus paradoxus in asthma. If however there was a pCO_2 of > 40mmHg, then the mean pulsus paradoxus was significantly higher than if pCO_2<40. Shim and Williams (354) also showed in a population of adult asthmatics that although the presence of pulsus paradoxus was associated with more severe airway obstruction, pulsus paradoxus was present with relatively mild airway obstruction and was sometimes absent in the presence of severe obstruction. Similarly Lewis et al (355) showed that although the presence of pulsus paradoxus correlated with severe asthma, an exhausted patient did not have a pulsus paradoxus despite severe airways obstruction. In a national study of inpatient asthma in England (356), 766 patients were admitted and pulsus paradoxus was recorded in 314, with 142 having a paradoxus of 10mmHg or more. Paradoxus of 10mmHg or more was found in 21 of 68 patients with peak expiratory flow (PEF) >200L/min, 62 of 139 with PEF 100-200L/min and 53 of 83 with PEF of <100L/min. When paradoxus was ≥25mmHg PEF was always low. Notably there were 14 patients admitted with paradoxus of >10 as the only abnormal feature on admission, and none of these required ventilation or ICU admission. They concluded that pulsus paradoxus was a poor guide to the severity of acute asthma in individual patients. Other studies will be required to assess the reliability of pulsus paradoxus as a marker of severe croup. In particular it may be useful to use objective measures of pulsus paradoxus rather than the clinical assessment of whether a palpable paradoxus is present or not.

The Klein score refers to active abdominal muscle contraction at the end of expiration, but it is possible that there may a number of mechanisms for abdominal muscle contraction, and I have been unable to find literature to support this clinical feature. As shown in figures 6.2 and 6.4, the oesophageal pressure does tend to rise towards the end of expiration in patients with croup, in contrast to the normal control (figure 6.1) and this may be related to abdominal muscle activity.

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The interobserver variability in the assessment of clinical signs in pediatric post-extubation stridor was assessed by Kemper et al (109). Of the parameters assessed by a variety of staff in the 5 minutes following 27 extubations of 25 children less than 15 years of age (median age 7 years) respiratory rate and flaring/retractions were found to be relatively reliable (weighted Kappa statistic (K_W) >.61), while stridor and level of consciousness were only moderately reliable (K_W .40 to .60). Agreement about air movement was no different from that expected by chance alone (K_W < .4).

There is very limited literature available regarding overall (as opposed to individual component) agreement between raters. In a study of patients with croup (189), which used the Westley score, it was reported that the agreement between raters was high (weighted kappa value 0.9; 95% confidence interval, 0.8 to 1.0).

As pointed out by Chan et al (132), reports of score reliability in the research setting are generally higher then when used in the clinical setting, one of the reasons possibly being the range of observers, and the level of training that they have received.

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8.5.2 Utilization of scores

Scoring systems have been (and are) used for a variety of purposes, including research studies (to provide some measure of both severity of illness and response to therapy), and in clinical practice (to direct patient care). In the research setting a large number of studies (as shown in Chapter 2) have demonstrated clinical responses to therapy, but a concern regarding these studies is whether that change in score really has clinical relevance or significance. It is not clear in scales that may have a range of up to 18 points, whether a) different patients with the same score have the same severity of illness or b) whether a change in the score actually reflects a change in overall clinical condition, particularly when there may be up to 18 points within the score (it seems unlikely that clinical scores have that degree of discrimination).

In clinical practice the real question is often not whether the patient improved but whether the patient improved to the point where they can be sent to a ward rather than to intensive care, or where they can be sent home rather than kept for ongoing evaluation? Thus for clinical utility scores need to be validated, with cut-off points for interventions, and that does not appear to have happened for croup scores.

It is a feature of the data presented in chapters 6 and 7, that while some parameters (e.g. those related to airflow and volume), can clearly differentiate between patients with croup and control patients, those same parameters cannot be used to differentiate between different levels of severity of croup. It would seem unlikely that a single set of clinical signs can be used reliably to assess the severity of disease over an entire clinical spectrum. At the same time the requirements for a clinically relevant scoring system would be that: the components are clear, defined and easily measurable; there are as few components as possible; the calculation of the score must be straightforward; there must be clear guidelines for the appropriate response to specific levels of scores.

While there are many scores available, very few have been evaluated against these criteria. The Klein Score has been used extensively in Cape Town, South Africa, and although the data has not been published, it is simple and thought to be reliable in predicting the need for endotracheal intubation (since implementation there have been hardly any cases of "unexpected collapse" in croup patients) (M Klein – personal communication). It is possible that using this score with the associated management plan, more children than entirely necessary receive endotracheal intubation, but this may be an acceptable balance.

8.6 Conclusions

Although there are many clinical scoring systems reported for the assessment of the severity of croup, there is extremely limited information available regarding the validity and optimum utilization of these scores. Many of the parameters used in clinical scores are poorly defined, and may have limited relevance in croup. Despite

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the widespread use of these scores for clinical practice and research studies, there is a need for the scores to be validated and compared with objective measures of disease severity and outcome. In addition the interpretation of scores and associated recommended therapeutic interventions requires re-evaluation.

Chapter 9
Comparison between objective measures of croup severity and the Klein croup score.

9.1 Introduction

As outlined in the initial literature review, and subsequently in the chapter on assessment of severity in croup (Chapter 8), there is very limited published data available on the relationship between clinical scores and objective measurements of airway obstruction or of disease severity in croup.

In this section, clinical data (Klein score) was compared with measurements of croup mechanics of breathing taken at that time. At the time of the study the Klein score was in routine use as the scoring system for croup at the Red Cross War Memorial Children's Hospital in Cape Town.

A secondary component of this study was a comparison of clinical features such as saturation and the presence or absence of cyanosis with objective measures of severity of airway obstruction.

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9.2 Patients and groups

Data on clinical components for the Klein score (presence of stridor during inspiration and expiration, presence of palpable pulsus paradoxus and presence of active abdominal expiration) was collected during the data collection for baseline studies and following nebulization with adrenaline. All clinical data was collected by the same observer (AA).

The details of the measurement of airway mechanics in all these studies are provided in the Patients and Methods chapter (Chapter 4).

The overall data from patients in different clinical grades was analyzed, and subsequently data was analyzed from patients who had undergone adrenaline nebulization, and had been noted to change clinical grade in the time period following that nebulization.

Data for all traces with full associated clinical data was analyzed as a group.

Data for baseline traces on all patients was compared using the objective measures of respiratory mechanics and clinical signs collected.

9.3 Results

9.3.1 Overall patient data

There were a number of problems with the analysis of the data related to the grading system because of apparent discrepancies between the presence of pulsus paradoxus and active abdominal expiration. One patient (16) had a period when there was both inspiratory and expiratory stridor, no pulsus paradoxus, but active abdominal expiration was present. The severity of airway obstruction as measured by objective measures in this patient was comparable to those patients with grade 3 airway obstruction. Another patient (17) had a period when there was inspiratory but no expiratory stridor and no pulsus paradoxus, but active abdominal activity. At this time the severity of airway obstruction was much more compatible with other grade 0 or 1 patients

Data from all the traces shows no differences in respiratory rate data (including respiratory rate, IE ratio, inspiratory and expiratory times) between the groups of clinical grades (Table 9.1). Likewise there was no significant difference between flow and volume data on the clinical grades (Table 9.1).

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Table 9.1 Data on all traces with clinical data available

	Clinical grade				
Variable	**0**	**1**	**2**	**3**	**p value (Kruskal -Wallis)**
N =	**3**	**9**	**21**	**102**	
Respiratory rate data					
Respiratory rate (b/min)	32 (7.7)	31 (9.5)	33 (9.4)	34 (9.2)	0.77
IE ratio	0.83 (0.18)	0.75 (0.25)	0.78 (0.13)	0.86 (0.12)	0.09
Inspiratory time (s)	0.84 (0.08)	0.81 (0.33)	0.80 (0.18)	0.82 (0.25)	0.74
Expiratory time (s)	1.02 (0.25)	1.07 (0.26)	0.999 (0.43)	0.93 (0.27)	0.51
Flow and volume data:					
Peak inspiratory flow (ml/s)	113 (13)	95 (31)	105 (24)	96 (32)	0.45
Mid inspiratory flow (ml/s)	98 (8)	79 (29)	100 (25)	91 (29)	0.31
Peak expiratory flow (ml/s)	102 (23)	65 (16)	86 (18)	86 (27)	0.07
Mid expiratory flow (ml/s)	89 (21)	60 (20)	74 (21)	77 (27)	0.107
Tidal Volume (ml/kg)					0.09
Minute Ventilation (ml/min/kg)	260 (25)	184 (57)	218 (68)	202 (60)	0.06
Pressure data					
ΔPoes (cm H_2O)	**15 (3)**	**30 (10)**	**43 (21)**	**67 (24)**	**<0.0001**
Indices derived from Flow-volume data					
AFV (ml/s.ml/kg)	1216 (122)	935 (395)	951 (270)	907 (449)	0.18
Tmif / Titot (%)	79 (20)	75 (8)	62 (12)	63 (18)	0.08
Tmef / Te_{TOT} (%)	**33 (3)**	**58 (35)**	**76 (39)**	**76 (20)**	**0.019**
Indices derived from Flow-pressure data					
$R_{AW}0.5_I$ (cm H_2O/ml/s)	**70 (20)**	**162 (51)**	**217 (120)**	**342 (218)**	**< 0.0001**
$R_{AW}0.5_E$ (cm H_2O/ml/s)	**51 (6)**	**199 (61)**	**220 (79)**	**251 (147)**	**0.0004**
C_L (ml/cm H_2O/kg)	1.45 (0.11)	0.74 (0.37)	1.10 (0.60)	1.17 (3.28)	0.396
Indices of effort					
Pressure Rate Product (cm H_2O/min)	**434 (97)**	**710 (174)**	**1000 (1180)**	**1824 (1068)**	**<0.0001**
Pressure time integral (cm H_2O.s/min)	**284 (76)**	**596 (605)**	**801 (333)**	**1235 (463)**	**<0.0001**
Work of breathing (gm.cm/kg)	**73 (18)**	**126 (75)**	**220 (81)**	**262 (135)**	**<0.0001**
Rate of work of breathing (gm.cm/min/kg)	**2706 (759)**	**3920 (1456)**	**7066 (3011)**	**9574 (4815)**	**<0.0001**
Volume for Effort (ml.cm/H_2O/s)	**7.6 (1.7)**	**3.0 (0.7)**	**2.5 (1.1)**	**1.6 (0.9)**	**<0.0001**

Data as mean (sd)

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There were significant differences in ΔPoes with ΔPoes rising progressively from 15 (3) H_2O in grade 0 traces through to 67 (24) cm H_2O on grade 3 traces. These patterns were present on $R_{AW}0.5_I$, $R_{AW}0.5_E$, Pressure Rate Product, Pressure Time Integral, Work of breathing, and Rate of work of breathing . Mean Volume for Effort showed a progressive decrease from 7.6 (ml/cm H_2O/s) on grade 1 traces through to 1.6 (ml/cm H_2O/s) on grade 3 traces. However there was clear overlap between grades for values of all these indices.

Among the indices derived from flow-volume data Tmef / Te_{TOT} (%) showed clear trends from 33 (3) in grade 0 through to 76 (39) and 76 (20) on traces on grade 2 and 3 respectively. A striking feature of Tmef / Te_{TOT} (%) is that there is large difference from grade 0 to grade 2, but minimal difference between grades 2 and 3.

A more limited set of data was collected at the time of baseline studies on 18 patients and is shown in table 9.2.

Once again there was no difference between grade 2 and 3 data for all parameters relating to respiratory rate data, flow and volume data. Despite the low numbers of grade 2 traces, there was a significant difference between grade 2 and grade 3 traces as regards $R_{AW}0.5_I$, Pressure Time Integral and Volume for Effort while ΔPoes (median 38.5 vs 79.3) approaches statistical significance (p=0.056). On indices derived from flow volume data there was also a significant difference between grade 2 and grade 3 traces for Tmef / Te_{TOT}.

It is striking that there is approximately a 2-fold difference between mean values related to oesophageal pressure change for grade 2 and 3, while there are minimal changes in flow and volume data.

It is clear that there are a wide range of values related to oesophageal pressure change for patients with grade 3 clinical features.

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Table 9.2: Clinical grade and measured data on patients at baseline

	Clinical grade		
Variable	**2**	**3**	**p value (Mann Whitney)**
N =	**3**	**15**	
Respiratory rate data			
Respiratory rate (b/min)	34.3 (34.3 – 53.7)	36.2 (29.5 – 40.5)	0.82
IE ratio	0.84 (0.78 – 0.94)	0.84 (0.66 – 0.96)	0.91
Inspiratory time (s)	0.77 (0.51 – 0.87)	0.77 (0.50 – 0.96)	0.91
Expiratory time (s)	0.92 (0.61 – 0.98)	0.87 (0.65 – 1.19)	0.82
Flow and volume data:			
Peak inspiratory flow (ml/s)	89.2 (88.5 – 122)	96.4 (59.0 – 258)	0.74
Mid inspiratory flow (ml/s)	86.4 (72.8 – 120.3)	93.9 (52.7 – 256.7)	0.91
Peak expiratory flow (ml/s)	79.0 (63.1 – 102.4)	84.0 (50.3 – 200)	0.74
Mid expiratory flow (ml/s)	76.6 (55.8 – 98.3)	78.9 (42.3 - 197.4)	1.0
Tidal Volume (ml/kg)	5.59 (5.5 – 6.4)	5.47 (2.9 – 12.5)	0.49
Minute Ventilation (ml/min/kg)	215 (191 – 297)	176 (107 – 617)	0.36
Pressure data			
ΔPoes (cm H_2O)	38.5 (17.1 – 72)	79.3 (31.7 – 126.2)	0.056
Indices derived from Flow-volume data			
AFV (ml/s.ml/kg)	925 (735 – 1165)	698 (281 – 5304)	0.49
Tmif / Titot (%)	62.6 (61.7 – 66.9)	64.2 (36.7 – 83.3)	0.91
Tmef / Te_{TOT} (%)	**39.1 (35.9 – 66.8)**	**75.6 (41.6 – 92.1)**	**0.027**
Indices derived from Flow-pressure data			
$R_{AW}0.5_I$ (cm H_2O/ml/s)	**245 (136 – 295)**	**463 (175 – 872)**	**0.027**
$R_{AW}0.5_E$ (cm H_2O/ml/s)	207 (32 – 248)	228 (72 – 509)	0.10
C_L (ml/cm H_2O/kg)	1.1 (0.6 – 1.12)	0.75 (0.08 – 3.86)	0.74
Indices of effort			
Pressure Rate Product (cm H_2O/min)	1321 (575 – 3867)	2778 (1201 – 4673)	0.25
Pressure time integral (cm $H_2O.s.min^{-1}$)	749 (315 - 1476)	1518 (604 – 2298)	0.10
Work of breathing (gm.cm/kg)	113 (71 – 297)	161 (87 – 822)	0.16
Rate of work of breathing (gm.cm/min/kg)	5350 (2393 – 15933)	10226 (3291 – 40692)	0.36
Volume for Effort (ml/cm H_2O/s)	**2.46 (1.9 – 5.7)**	**1.38 (0.86 – 3.34)**	**0.027**

All data as median (range)

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9.3.2 Individual patient data

Data for both airways resistance and pressure rate product on individual patients is shown in Figures 9.1 and 9.2. For some patients changes in the severity of obstruction as assessed by the mid-inspiratory resistance and the pressure rate product parallel changes in the croup score, but for others the changes are not reflected.

The efficacy of breathing data from multiple traces on patients who were recorded as having more than 1 clinical grade during the study is displayed in figure 9.3. It can be seen that there is considerable overlap in the data for different grades on the same patients, as well as for different patients on the same grades of severity.

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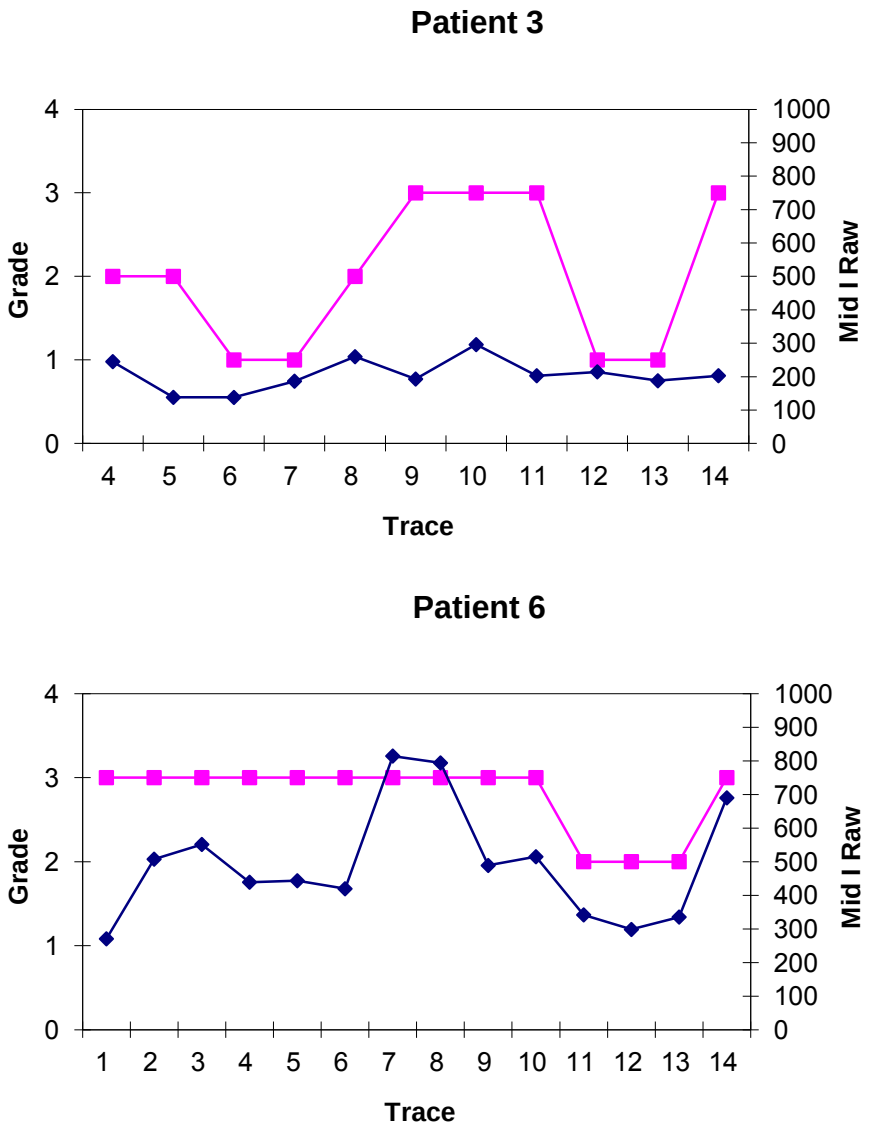
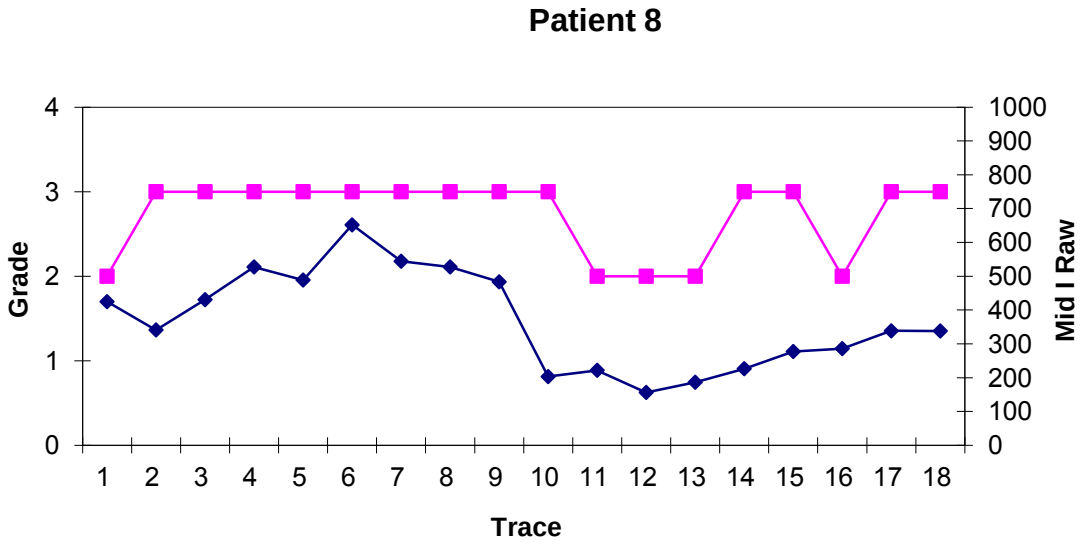
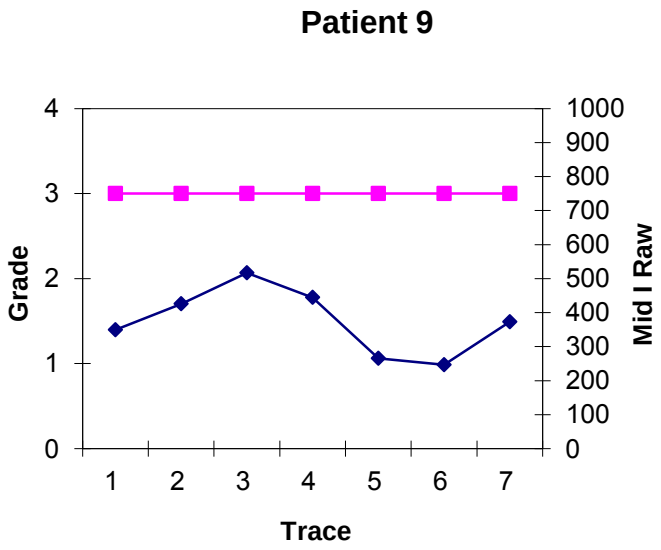
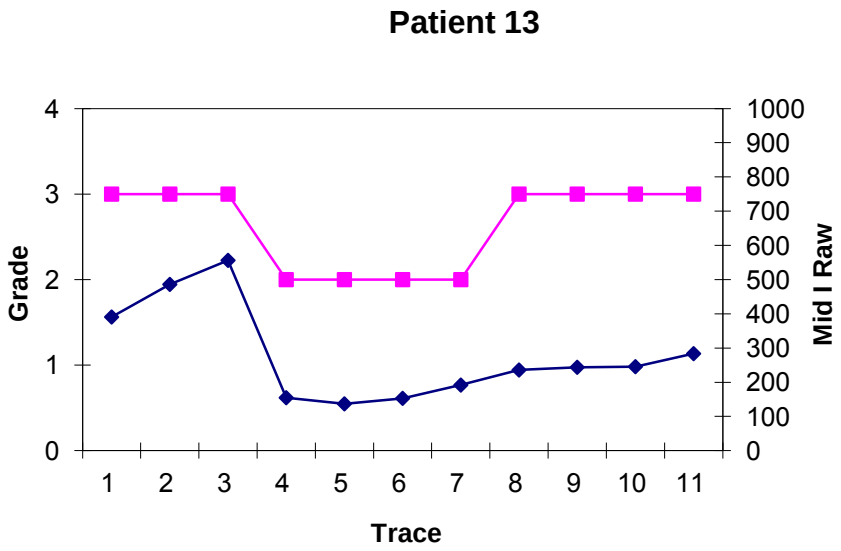
Figure 9.1: Mid inspiratory resistance and croup score (Klein) on patients who changed score during the course of the study

The croup score is shown in pink, while the associated mid-inspiratory resistance is shown in blue. Traces were done at 5 minute intervals. Changes were usually after nebulization.

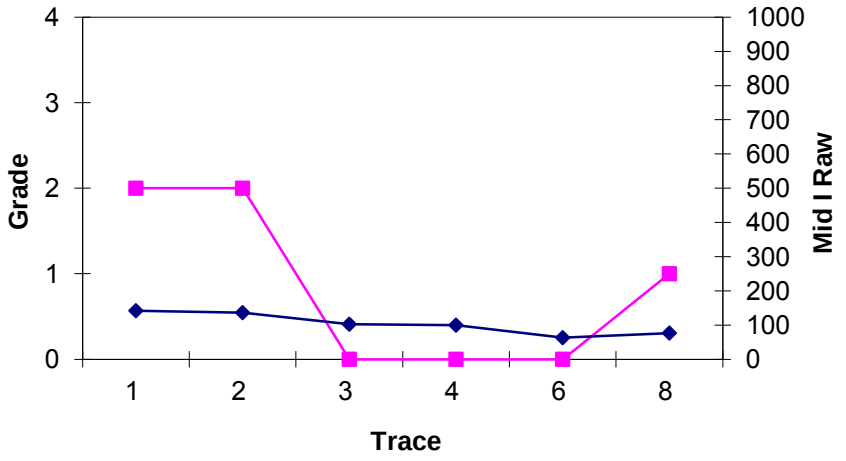



Patient 8
Grade
Mid I Raw
Trace
0
1
2
3
4
0
100
200
300
400
500
600
700
800
900
1000
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

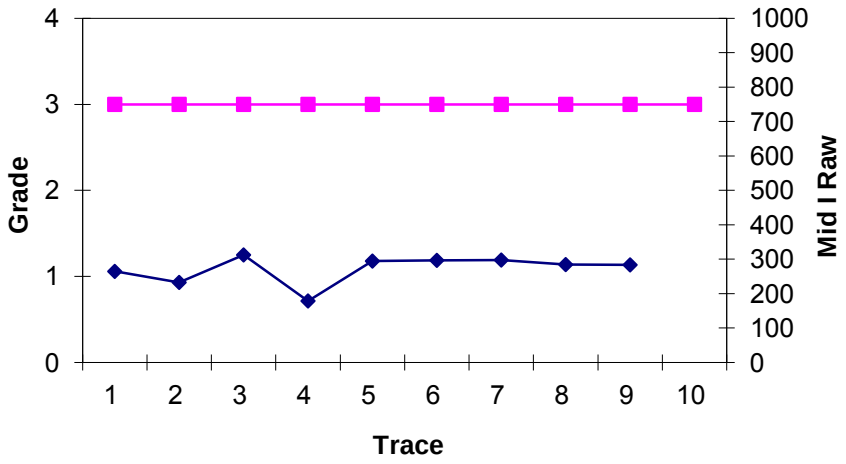

Patient 9
Grade
Mid I Raw
Trace
0
1
2
3
4
0
100
200
300
400
500
600
700
800
900
1000
1 2 3 4 5 6 7


Patient 13
Grade
Mid I Raw
Trace
0
1
2
3
4
0
100
200
300
400
500
600
700
800
900
1000
1 2 3 4 5 6 7 8 9 10 11

Patient 15



Patient 16



Patient 17

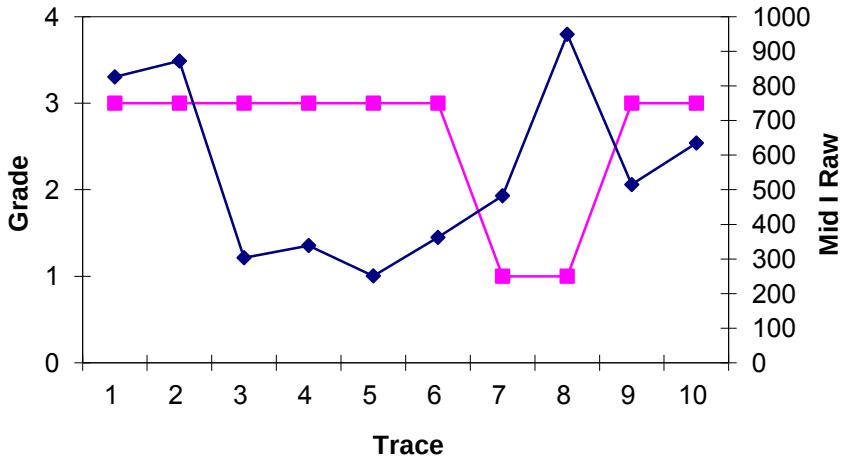
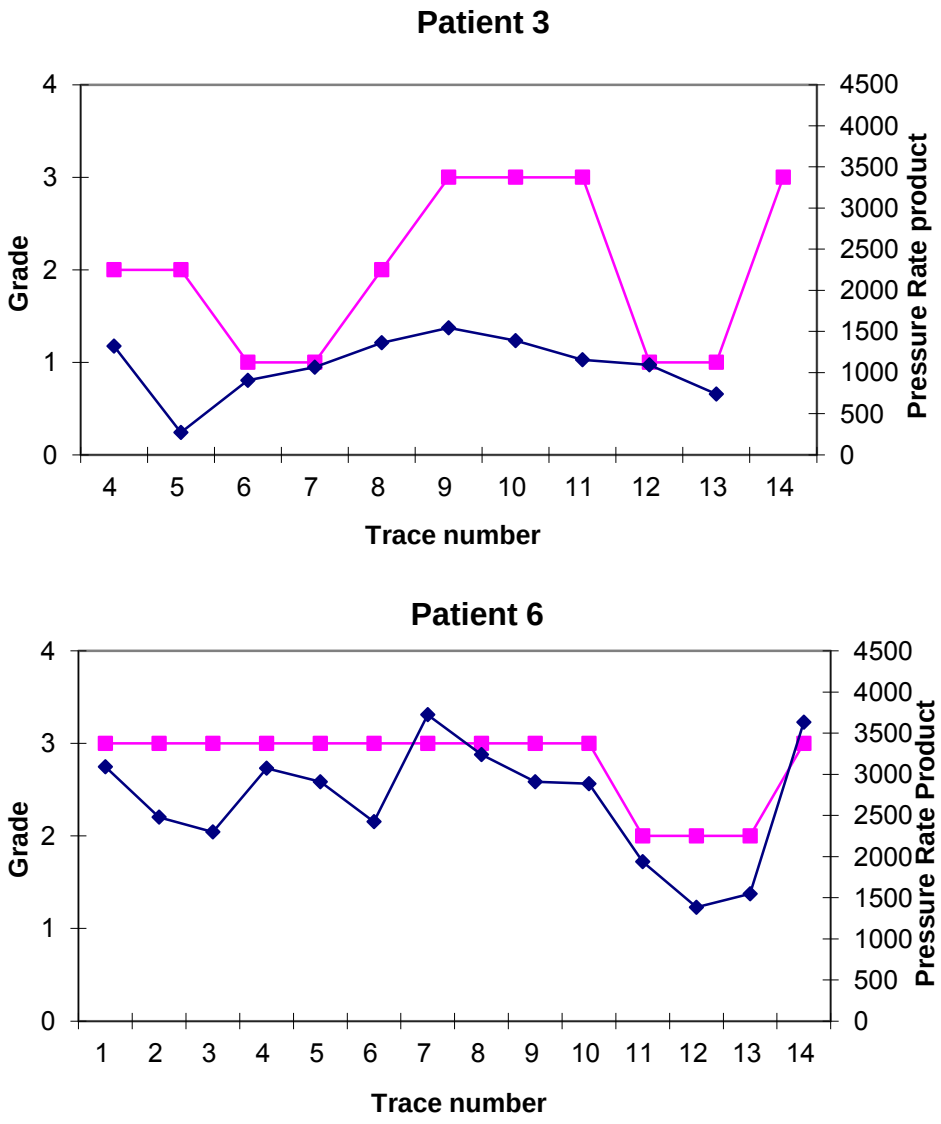
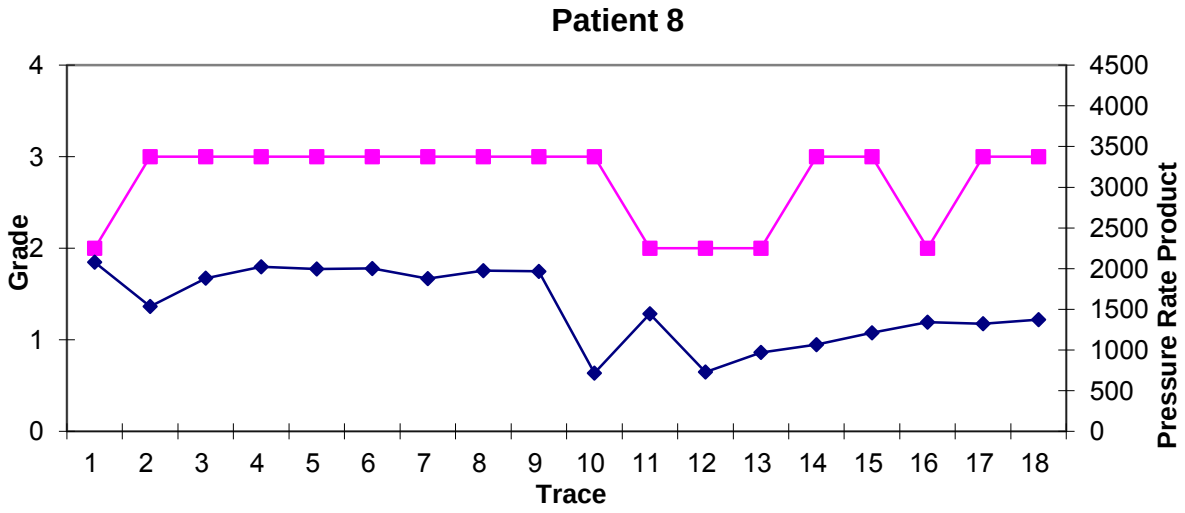


Figure 9.2: Pressure rate product and croup score (Klein) on patients who changed score during the course of the study

The clinical grade (Klein) is shown in pink, while the pressure rate product is shown in blue. Traces were done at 5 minute intervals. Changes were usually in response to nebulization.




Patient 8
Grade
Pressure Rate Product
Trace
0
1
2
3
4
500
1000
1500
2000
2500
3000
3500
4000
4500
1
2
3
4
5
6
7
8
9
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11
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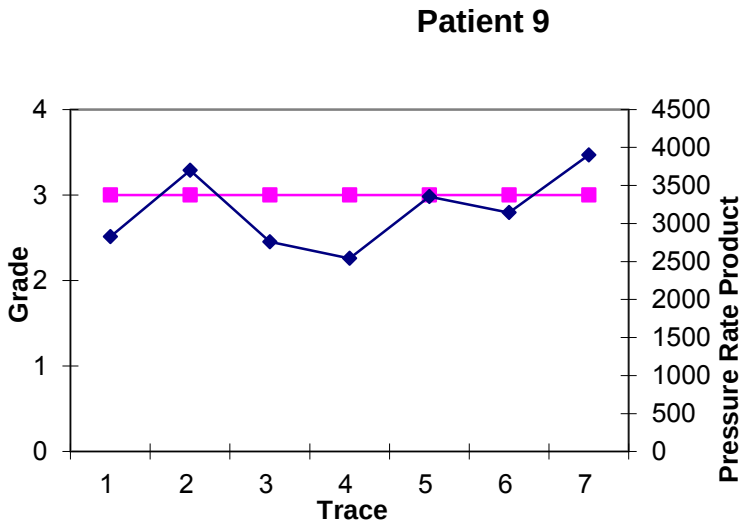
15
16
17
18


Patient 9
Grade
Pressure Rate Product
Trace
0
1
2
3
4
500
1000
1500
2000
2500
3000
3500
4000
4500
1
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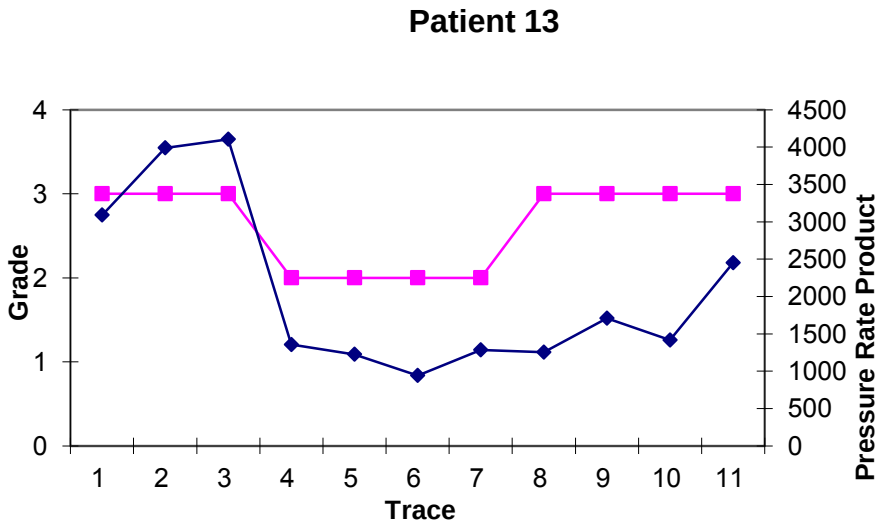
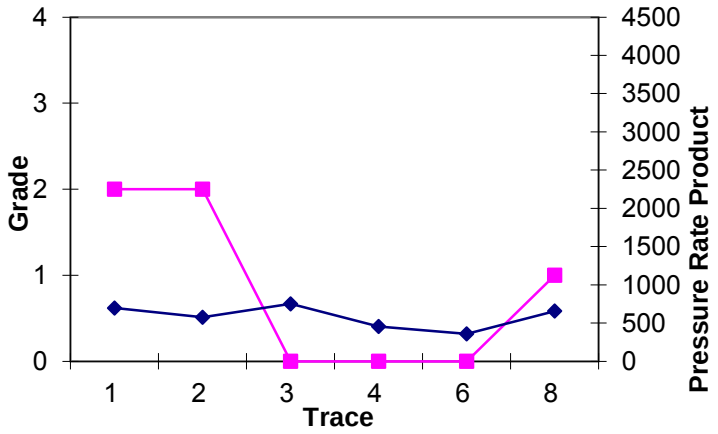
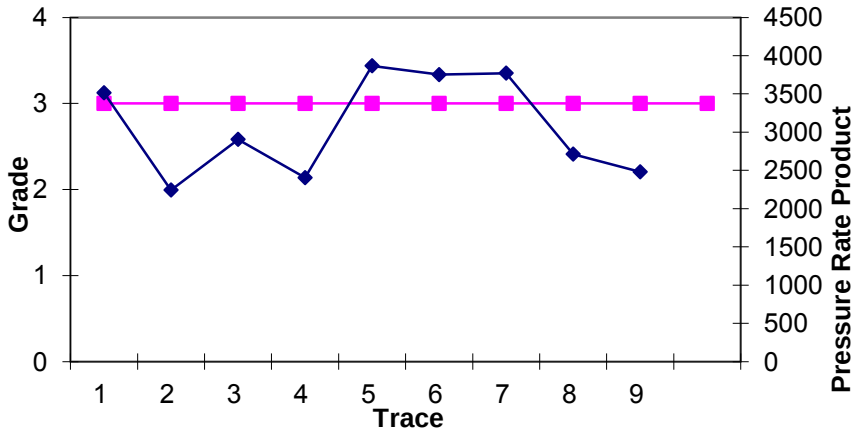
3
4
5
6
7


Patient 13
Grade
Pressure Rate Product
Trace
0
1
2
3
4
500
1000
1500
2000
2500
3000
3500
4000
4500
1
2
3
4
5
6
7
8
9
10
11

Patient 15



Patient 16



Patient 17

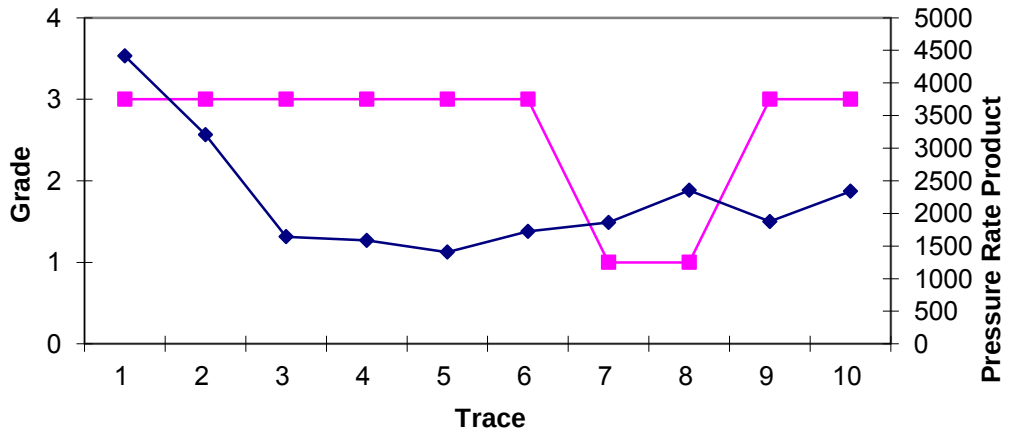


Figure 9.3: Efficacy of breathing data from individual patients.

Data from multiple traces on groups of individual patients is shown for Efficacy of breathing. There are varying degrees of overlap between efficacy at different grades.

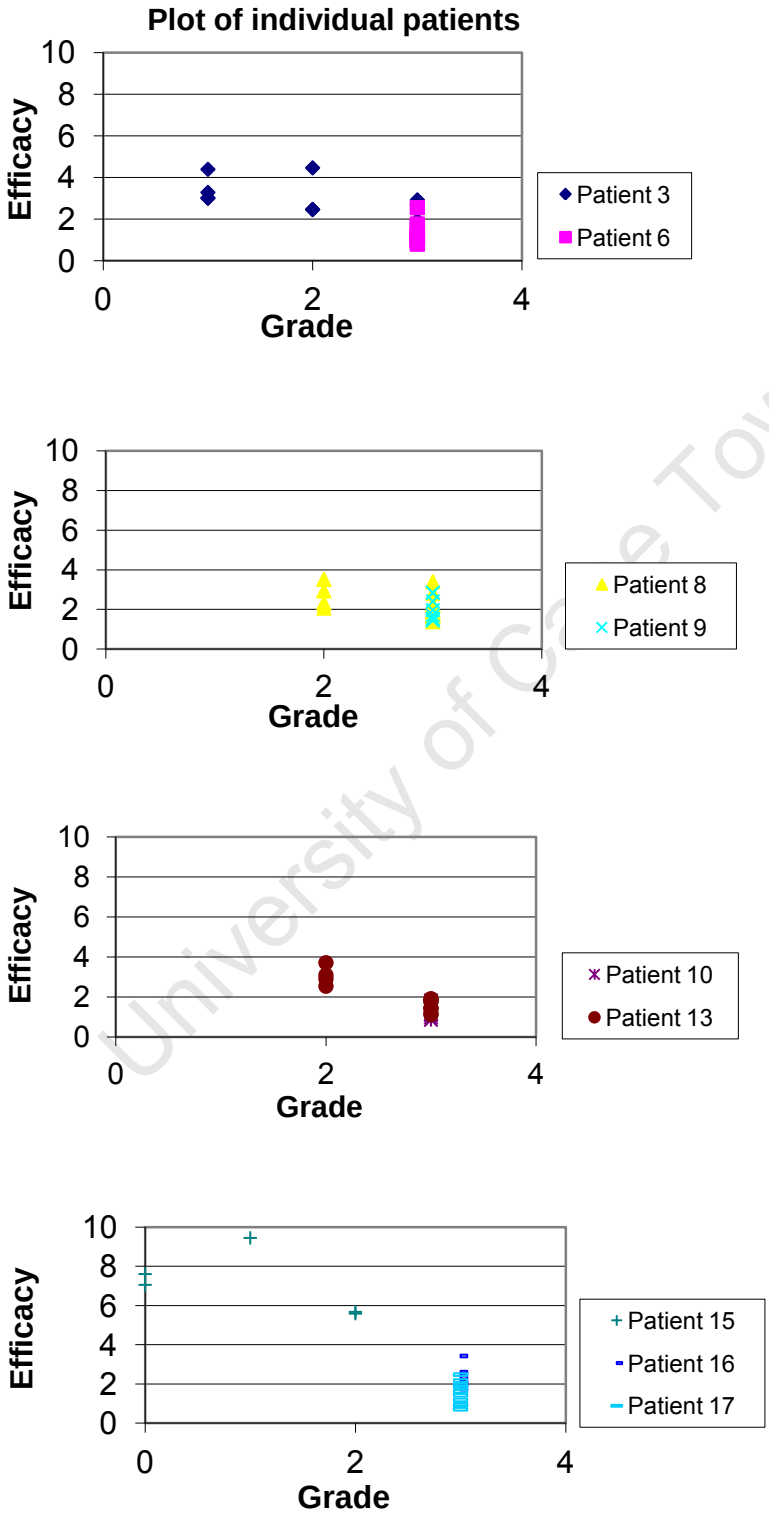


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Figure 9.4: Saturation (%) and severity of croup, respiratory rate and heart rate.

Data from all patients showing the relationships between oxygen saturation and clinical severity (Klein croup score), respiratory and heart rates.

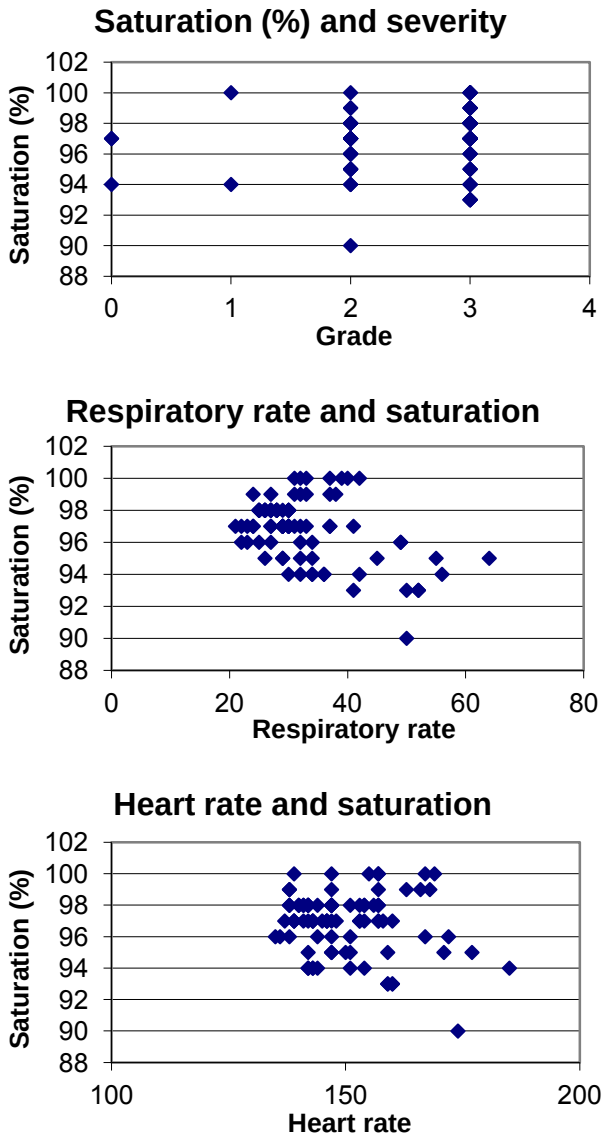

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Figure 9.5: Saturation and independent measures of severity of airway obstruction

Data from all patients showing the relationship between oxygen saturation and other measures of the severity of airway obstruction.

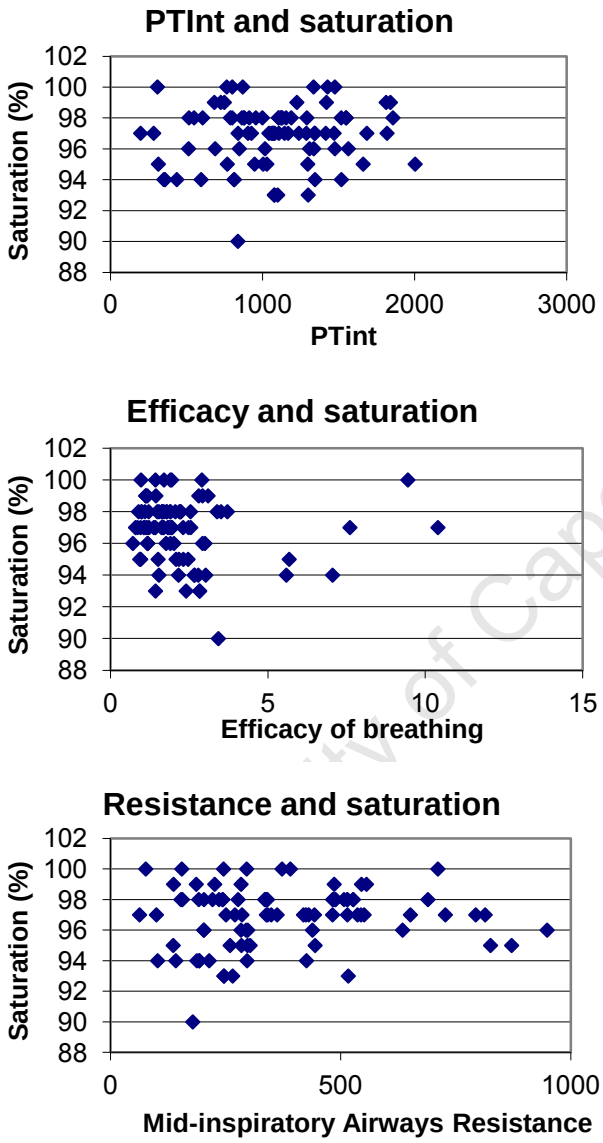

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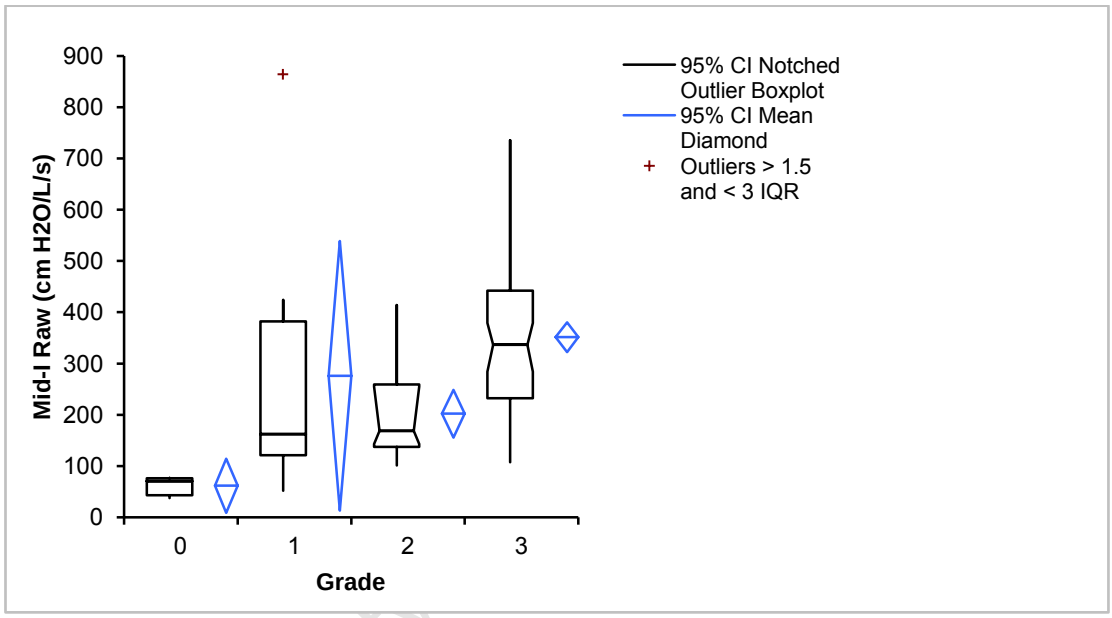
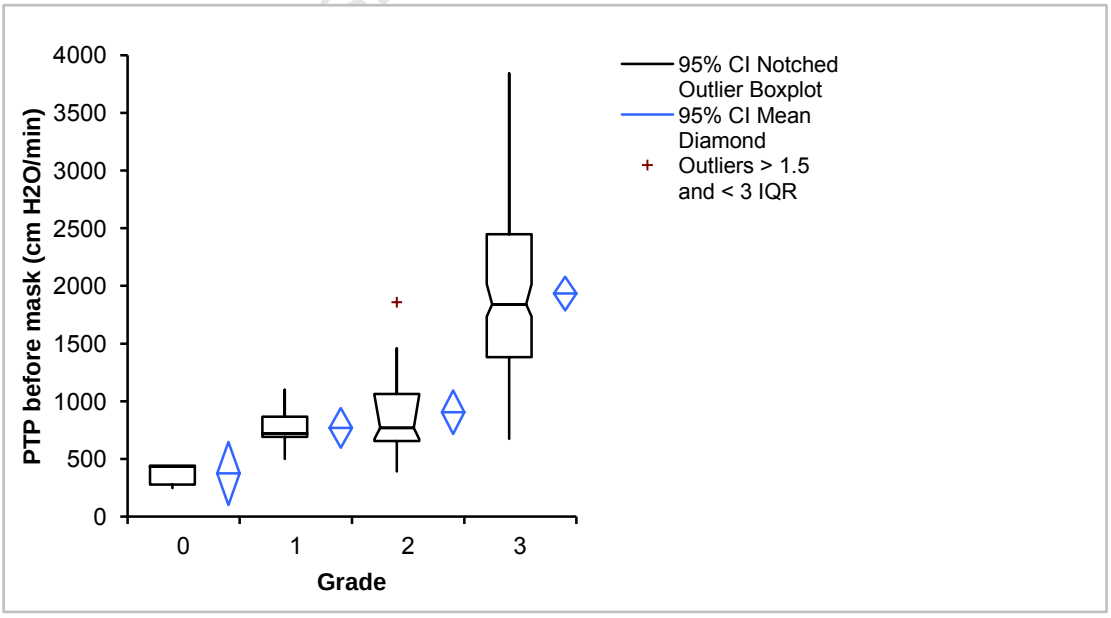
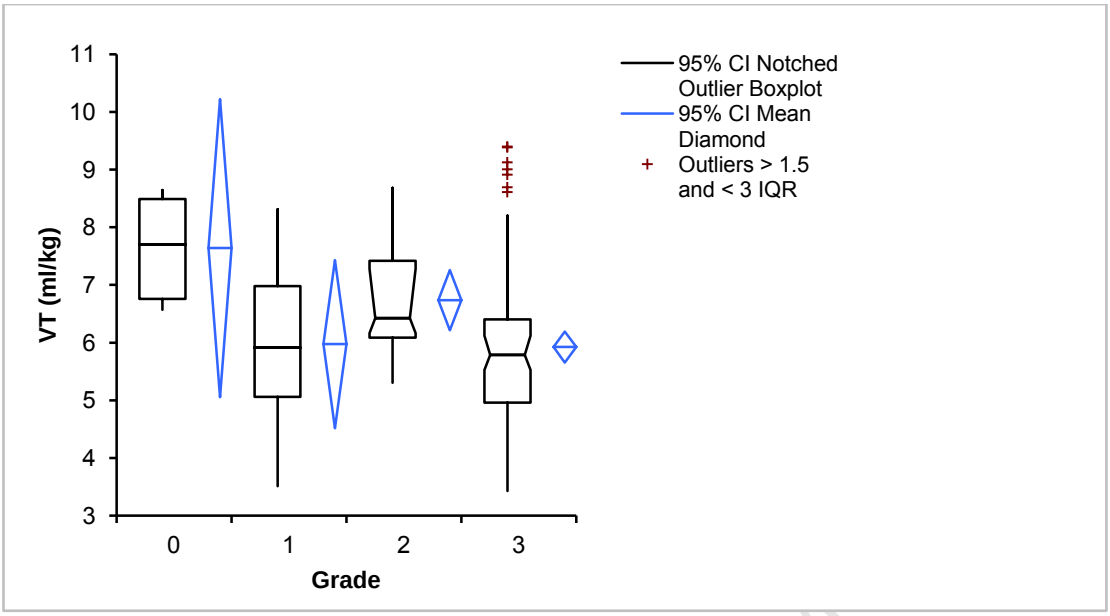
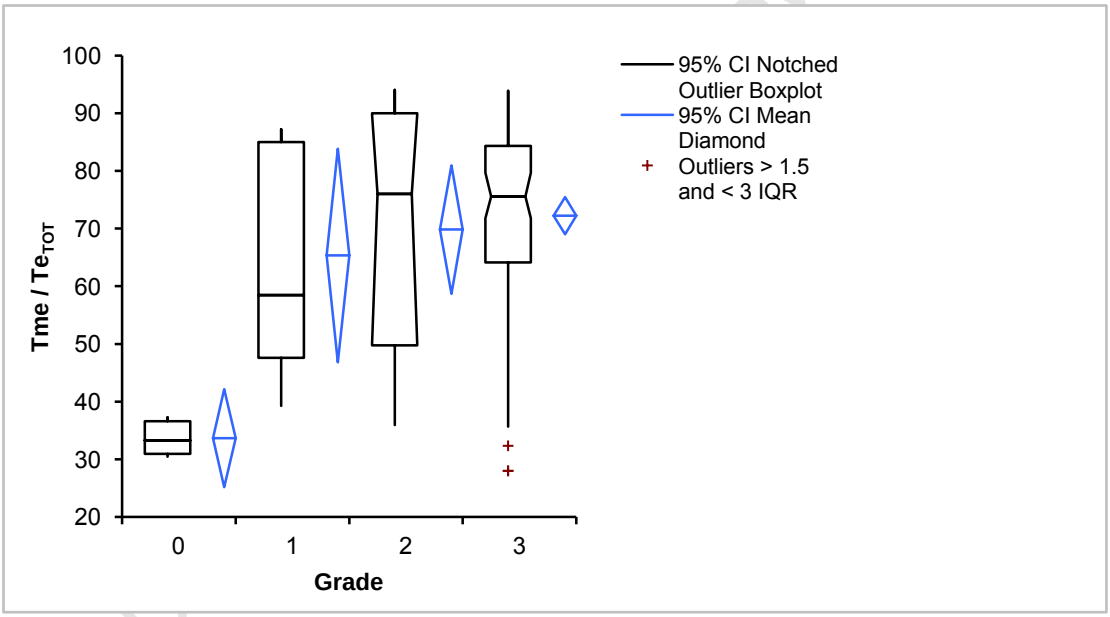
Figure 9.6: Change in parameters with grade

This figure shows a series of boxplots and mean and standard deviation plots of all clinical data on all patients, suggesting that parameters such as the mid-inspiratory reisistance and the pressure time product increase progressively with an increase in grade, while the parameters Tmef / Tetot (%) and tidal volume change markedly from normal to mild grades of croup but thereafter there is little change.









For all graphs: the blue plots represent the mean (horizontal bar) with the diamond extending to the upper and lower confidence intervals of the mean. The black plots are boxplots showing the median and the quartiles (the notches represent the confidence interval around the median) as horizontal lines. The vertical lines extend to the to the furthest observations within ±1.5 IQR (interquartile ranges) of the 1st or 3rd quartile. Observations within 1.5 IQRs and 3.0 IQRs are marked as near outliers +.

9.3.3 Clinical signs and severity scores

9.3.3.1 Oxygen Saturation

Only 1 patient had an oxygen saturation of <92% (90%) at the time of the baseline trace. Oxygen saturations on baseline data of patients with grade 2 and grade 3 clinical scores ranged from 93 to 100% (9.4). No patient had clinical cyanosis throughout all the studies, and during the 114 studies when saturation data was available the median (range) of saturations was 97% (90-100%).

As can be seen from figures 9.4 and 9.5 there was no relationship between saturation and clinical score, or other clinical parameters such as respiratory and heart rates. Neither was there a relationship between saturation and any of the measures of severity of airway obstruction including mid-inspiratory resistance, Pressure time integral or efficacy of breathing.

Heart rate and blood pressure showed no relationship with severity of croup as assessed by any criteria.

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9.3.3.2 Stridor

There were not enough patients without stridor to comment on the relationship between stridor and objective measures of airways obstruction.

However, throughout the studies there were no occasions when a patient with severe airway obstruction by any objective measure had no stridor.

9.3.3.3 Pulsus paradoxus

The presence or absence of pulsus paradoxus (i.e. changing from grade 2 to 3) did identify patients with a higher airway resistance. However there was overlap in airway resistance between patients with and without pulsus paradoxus, and on sequential studies, changes in pulsus paradoxus were not always followed by changes in objective measures of airway resistance.

9.3.3.4 Breath sounds

Although assessment of breath sounds was not part of the clinical evaluation of these patients, it is likely that the intensity of breath sounds is at least partially related to the air flow and tidal volumes. Figures 9.7 to 9.8 show that while measures related to intrathoracic pressure change show marked differences between patients with croup and normal controls, and can demonstrate clear changes in response to adrenaline nebulization in some patients, tidal volume and both peak inspiratory and expiratory flow rates do not differentiate between patients with croup and normal controls. In addition flow and volume changes are relatively small in response to adrenaline nebulization (see also chapter 6 for further discussion).

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9.4 Discussion

9.4.1 Review of objective measures of severity of croup

Data derived from oesophageal manometry is the clearest measure of the effort expended in breathing. However review of baseline data shows that pleural pressure changes are related to age. Animal data with imposed inspiratory resistance, (225) suggests that as airways obstruction increases, pleural pressure changes increase up to a point, beyond which the pressure changes may decrease with increasing obstruction as the respiratory system fails. This would also be in keeping with the data from asthma, where pulsus paradoxus has been associated with severity of asthma (352,357-359), but pulsus paradoxus may not be present in patients with very

severe asthma (356) . This would suggest that although the responses of individual patients could be monitored using oesophageal manometry, it would be difficult to set absolute values that indicate the need for intervention.

The presence of flow limitation in all patients with severe croup (chapter 6) suggests that flow and flow related measurements might not be appropriate measures of the severity of airways obstruction in croup. However baseline data (chapter 6) and responses to adrenaline nebulization (chapter 7) showed that 2 measures derived from flow volume analysis (namely the AFV and the T_{mef} / T_{eTOT}) might be useful measures of severity of airway obstruction. Both clearly differentiated between croup and normal, but T_{mef} / T_{eTOT} did not help to differentiate between different levels of severe croup.

Data shown in fig 9.6 again shows the effect that measures related to oesophageal pressure appear to increase in a linear fashion in association with increasing grade. While flow and volume related measures are able to differentiate between normal and croup, they do not clearly differentiate between different levels of severity.

Data derived from simultaneous measures of air flow and oesophageal pressure changes would provide an alternative objective assessment, although this has the disadvantage of added complexity. Measures of the work of breathing are not helpful (chapters 6 and 7) and have the theoretical problem that as airway obstruction gets worse a reduction in tidal volume will be reflected as a decrease in work of breathing, while effort of breathing may actually be increasing.

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Figure 9.7: Plot of flow and volume data showing responses to adrenaline nebulization

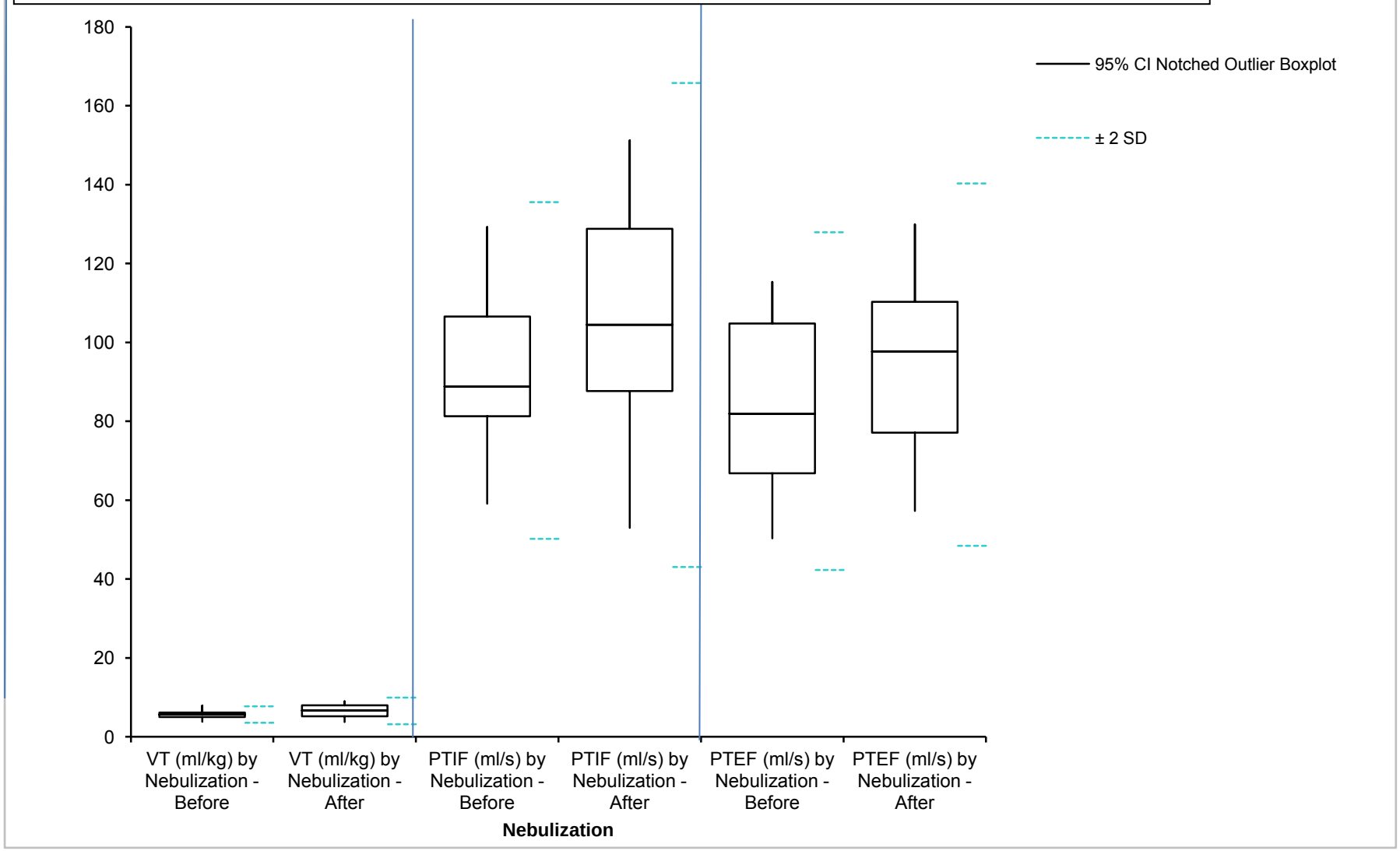


Figure 9.8: Plot of flow and volume data from patients with croup and normal controls

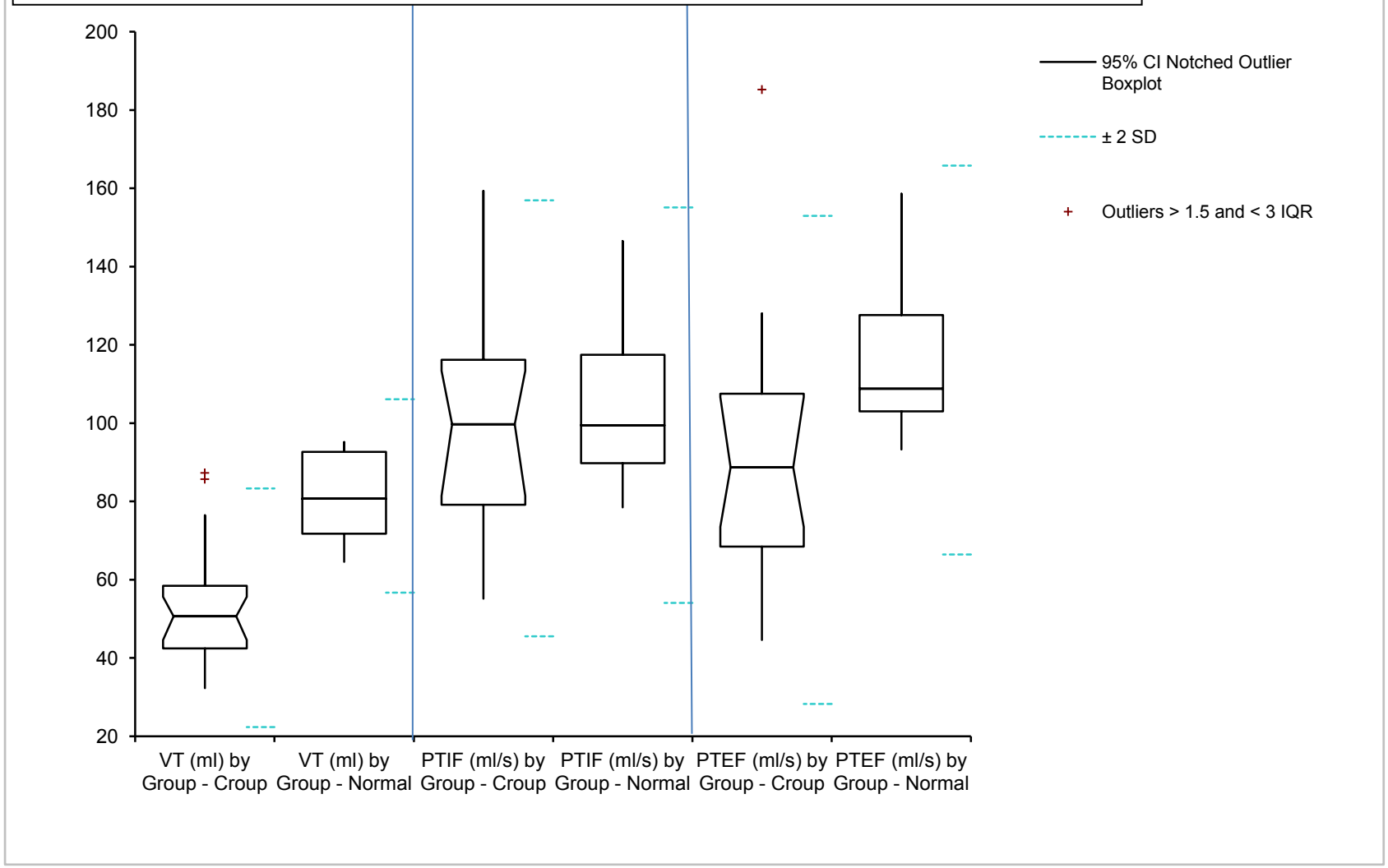


Figure 9.9: Plot of oesophageal ΔP and mid-inspiratory resistance data before and after adrenaline nebulization

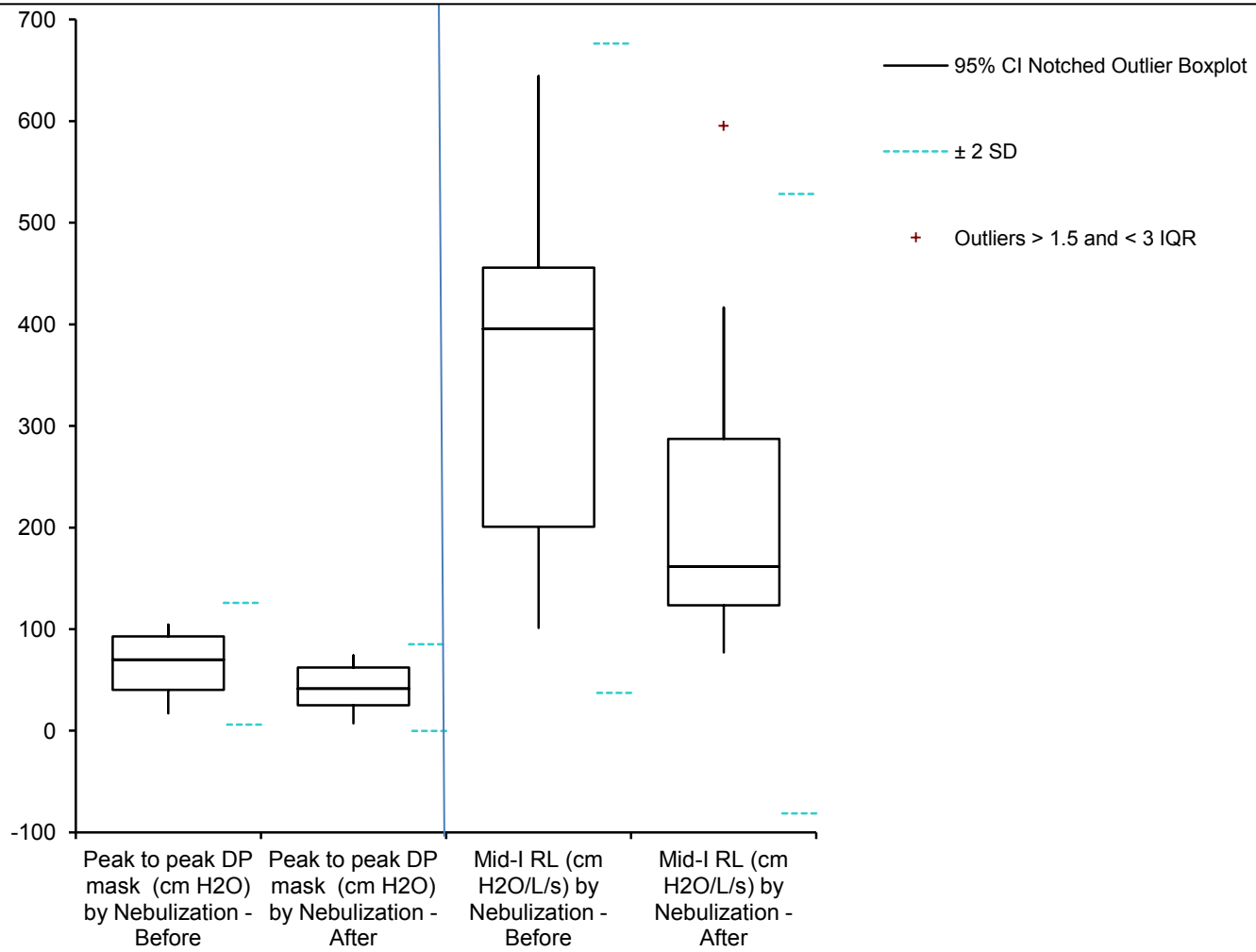
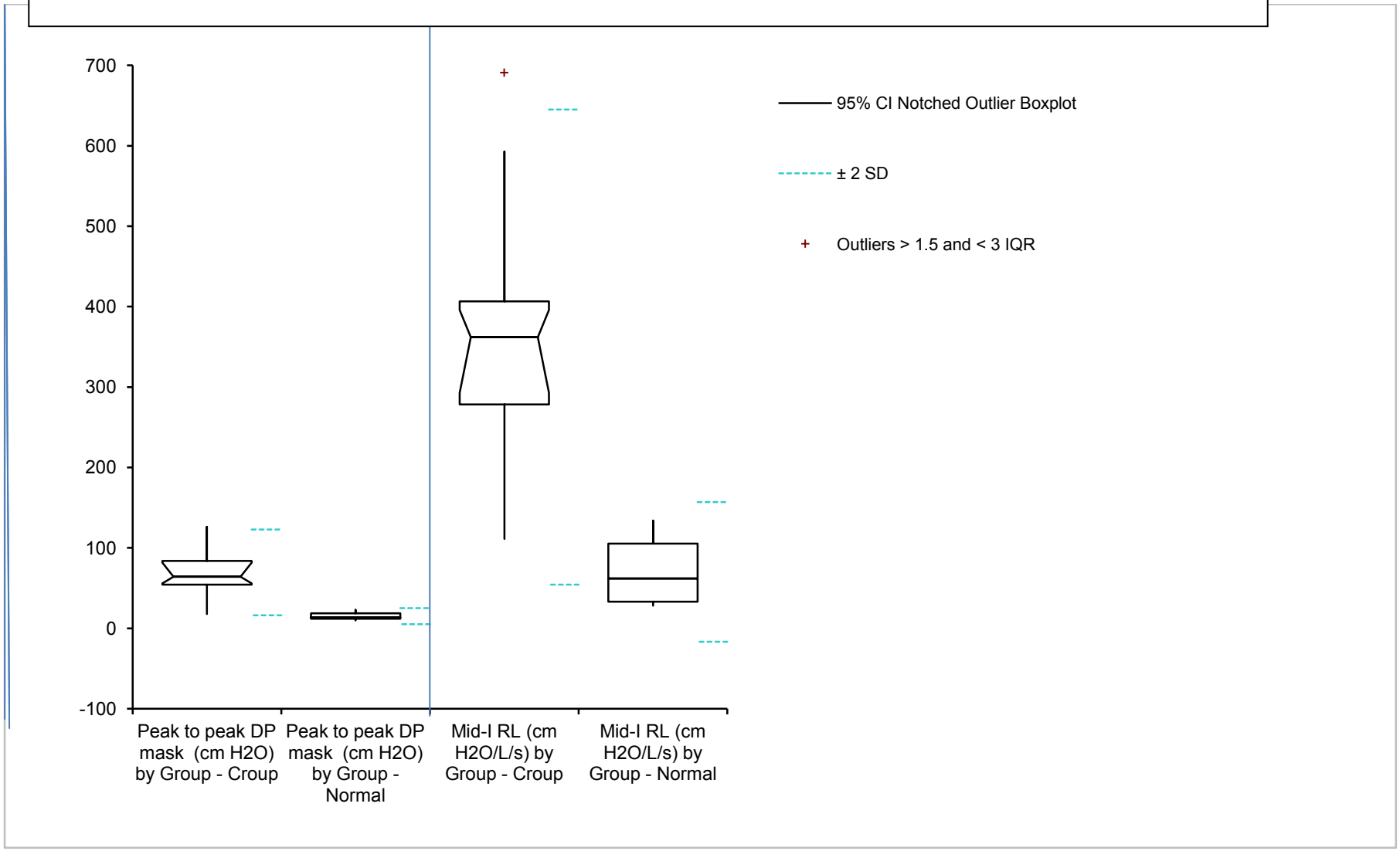


Figure 9.10: Plot of oesophageal ΔP and mid-inspiratory resistance data from normal and croup patients



The most direct measure of the severity of airway obstruction in croup is the measurement of airways resistance. However the respiratory mechanics data in croup (chapter 6) shows that there is variable airways resistance in croup, particularly during the inspiratory phase (with a progressive increase related to flow limitation). So measurement would have to be focussed on particular points such as mid-inspiration or mid expiration. In addition measurement of airways resistance requires the measurement of both flow and pressure changes and this may be difficult in critically ill children.

Sivan et al have previously shown that the Thoraco-abdominal asynchrony could be used to provide an objective measure of the severity of airways obstruction in croup (125). Thoraco-abdominal asynchrony has been validated against experimental imposition of measured inspiratory resistance in an animal model (139) Anaesthetized Rhesus monkeys were subjected to increased fixed inspiratory resistance (different to croup where there is variable and increasing inspiratory resistance and also increased expiratory resistance). There was a continuous increase in phase angle from 22^{o} at baseline to 165^{o} at 1000 cm H_2O/L/s, but the biggest change occurred in the range of 0-200cm H_2O/L/s. One monkey could not tolerate the 1000 cm H_2O/L/s resistance and showed a marked increase in end-tidal pCO_2. Saturation was constant with significant drop only at 1000 cm H_2O/L/s. The oxygen consumption did not increase over the period of the study. There was a gradual increase in pCO_2 with increased load, but poor correlation with phase angle measurements and also with the imposed load.

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Previous studies have not shown blood gas analysis to be useful in prediction of outcome of croups although patients with severe croup are more likely to be hypoxic and / or hypercarbic (135,137)

9.4.2 Klein score

The Klein score was used as a clinical score in this study, because that was the score that was used on all clinical patients at the Red Cross War Memorial Children's Hospital at the time (it is currently still the score in use). Other scores were not evaluated at the time and this was a missed opportunity. Unfortunately there were not enough patients with mild croup admitted to this study to provide meaningful data on the efficacy of the Klein score at the milder end of the spectrum.

A number of instances were identified where there was confusion regarding the presence of pulsus paradoxus and active abdominal activity on expiration. If this was a common occurrence, this would constitute a significant problem with the system. This can only be assessed by clinical review of more patients.

Data from the baseline studies showed that the Klein score identified patients with higher airways resistance and higher effort of breathing (as assessed by the Pressure rate product and the pressure time integral) although there was some overlap of the data.

Data from sequential studies in individual patients following nebulisation (with saline or adrenaline) however suggested that changes in the croup score were not reliably associated with the expected changes in the objective measures of airway

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obstruction. In some patients a change in the croup score was not reflected in a change in the objective measures, while in others substantial changes in objective measures were not reflected by changes in the croup score.

A Klein score of 3 was associated with significant airway obstruction, however the score provided little information regarding the severity of airway obstruction in patients in that group. Within the Klein grade 3 group, there was a wide range of severity of airway obstruction, with no clinical signs that correlated with those differences in objective measurements.Thus if a sustained score of 3 was taken as an indication for endotracheal intubation, it is likely that a number of patients would have been intubated when it was not indicated. However if the clinical priority was to ensure that every child who required intubation received intervention timeously, it might be acceptable if a number of children were intubated who would have coped without endotracheal intubation.

Although the Klein score appears to correlate with increasing severity of airway obstruction overall, there was overlap between the severity of obstruction at each clinical grade, and the score was not able to identify changes in severity of airway obstruction adequately.

This does raise the possibility that measurement of respiratory mechanics in patients who have been identified as having more severe croup may add to the quality of care in the intensive care environment.

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9.4.3 Other scoring systems

Although this investigation only directly looked at cyanosis (or pulse oximetry) stridor and pulsus paradoxus as clinical signs of severity of croup, it also indirectly provided information regarding respiratory rate, inspiratory and expiratory time, flow and tidal volume (which may relate to intensity of breath sounds).

Although hypoxaemia (by measured pO_2) has been well documented in patients with severe croup, there was clearly no relationship between severity of airway obstruction and hypoxaemia (as measured by pulse oximetry) demonstrated in this study. It is possible that data would be different at higher altitudes, and with other respiratory infections.

If we use the flow and tidal volume data as a proxy for air entry, then there is not much evidence to support this as a scoring feature, as there was no difference in flow and tidal volume between patients of varying clinical severity (by Klein score). Nor was there a significant difference in flow and tidal volume data following adrenaline nebulization in patients where there was a substantial decrease in airways resistance and in pressure time integral (which is not related mathematically to flow or volume in any way). In addition "air entry" has not been shown to be a reliable reproducible clinical sign between observers (109)

Pulsus paradoxus has previously been suggested by Steele et al (118,144), and there is reasonable evidence from this data that if pulsus paradoxus is present, then there is severe airway obstruction (with the proviso that if a patient were to become

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exhausted, then the effort expended and the pulsus paradoxus may decrease without implying an improvement in clinical condition).

9.4.4 The clinical utility of croup scores

Although croup scores have been extensively used in clinical trials to assess responses to therapy, the clinical challenge is whether a score can be safely used to monitor patient severity of illness and to predict the need for a clinical intervention such as: hospital admission; intensive care unit admission; endotracheal intubation etc. There is no reported literature to assess the utility of a score as a clinical tool.

It is clear that although the Klein score appears to increase in parallel with increases in measures of severity of airway obstruction, there is considerable overlap between groups. In addition the "grade 3" group includes a very wide range of severity of airway obstruction.

It is likely that clinical signs (or objective measures) do not vary in a linear fashion relative to the severity of airways obstruction, thus raising additional challenges in the design of clinical scoring systems with associated intervention levels. Finally the patient response to a gradual increase in severity of airways obstruction may also not be linear, and may have a "break" point after which the patient may decompensate.

9.5 Conclusions

Although this study was not designed to address the question of whether the Klein score is useful in the clinical scenario the data has confirmed that in patients with

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severe croup, the grades of the Klein score are associated with statistically different severities of airway obstruction. However there is overlap of the severity measurements within the grades and changes in either grades or severity of airway obstruction are not always reflected in the measures of airway obstruction or clinical grades. Further studies are required to validate this score in the clinical situation.

The data has also demonstrated that not all measurements of respiratory function change in a linear fashion over the range of croup severity.

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Chapter 10

Summary and future directions for research

The data presented in this thesis was collected in the early 1990s. Since that time there has been a significant change in the management of croup, particularly with widespread use of steroids. At the Red Cross War Memorial Children's Hospital the number of children admitted to the paediatric intensive care unit with severe croup has dropped from approximately 120 to 10-15 per annum. In Cape Town the management of croup has also been affected by the epidemic of Human Immunodeficiency Virus (HIV) infections (360). One of the consequences of these changes, is that clinical staff are seeing far fewer children with stridor, and the probability of a child with stridor having croup has changed (101). Thus clinicians are less likely to acquire skills of clinical assessment of airway obstruction in croup. In this setting there is a need for further development of clinical croup scores that are simple (using a few well defined parameters); reproducible when applied in the clinical setting; and reliable at prediction of both severity of airway obstruction and also clinical prognosis. There may also be an increased need for the development of simple measures of airway obstruction that can be applied at the bedside on unstable children, using equipment that is readily available in most paediatric intensive care units.

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10.1 Croup literature review

Although the clinical features, infective aetiology and pathology of croup have been well described over many years, there are:

Ongoing controversies regarding the appropriate nomenclature for patients with croup.

A wide range of clinical scoring systems that have been reported and used in both clinical and research settings. A review of these scoring systems showed that many clinical features were poorly defined; several clinical features used in scoring systems were unlikely to relate to the severity of

croup; very few clinical scoring systems had been systematically evaluated in terms of reproducibility and / or validity in assessment of severity of airway obstruction, prediction of clinical course (including need for hospital or intensive care admission; need for endotracheal intubation).

Very few studies have been published in which the mechanics of breathing in acute severe croup have been measured. In particular there are no published studies on intrathoracic pressure changes in patients with acute severe croup who have not been tracheostomized. Objective measures of severity of airway obstruction in croup are extremely limited.

Many studies have been published showing that steroids are associated with an improvement in clinical scores. This is supplemented by data showing that following the introduction of steroids for the management of croup, there has been a substantial reduction in the number of children requiring endotracheal intubation and / or intensive care admission.

Many studies showing that there are clinical improvements in patients with acute severe croup following the administration of adrenaline nebulization (either via nebulization with spontaneous breathing, or together with intermittent positive pressure breathing) have been published. The majority of those studies have relied on the use of clinical scores for the assessment of severity, and thus are potentially problematic (see above). There are a few studies showing objective improvement in respiratory function following the administration of adrenaline by nebulization.

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10.1.1 Future directions for research

It seems unlikely that there will be significant changes in the nomenclature for patients with croup. It is important that in both the clinical and the research settings, close attention be paid to careful use of the nomenclature with consideration of the particular pathological process present at a given time; the aetiological infective agents (both primary and possibly secondary infections); and contributory factors related to the patient's response to the infection. Failure to consider these factors

may lead to inadequate therapeutic responses and further confusion in the literature related to croup.

A concern with a significant part of the literature regarding both clinical therapy and the use of clinical scores is that clinical scores have been used as measures of response to therapy. Many of those scores have not been fully validated. In addition there is a concern as to whether a change in a clinical score is of clinical significance. This relates partly to the way in which scores are devised, but also to the way in which clinical scores are related to recommendations for clinical responses. Further research is required to assess this issue, and particularly as to whether changes in clinical scores are also related to safe and appropriate changes in clinical management. (see discussion related to clinical scores below).

If there is a change in the spectrum of viral infections related to acute severe croup (as may well happen with global climate change and the use of immunization), then there may be a need for further studies on the use of steroids in croup.

10.2 Methodology used in this study

10.2.1 Oesophageal manometry

During this study it was possible to obtain reproducible data from patients with acute severe croup documenting very large intrathoracic pressure swings. It was possible to do this with minimal disruption of the patients using a combination of topical analgesia with lignocaine, and sedation with chloral hydrate. Although there is increasing evidence that chloral hydrate may carry more side effects than was initially realized, there are other sedative agents that may be more appropriate now.

Oesophageal manometry can be performed using equipment which would be readily available in a paediatric intensive care unit, even in relatively poorly resourced parts of the world. The technique may not be accurate enough to detect subtle changes in

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respiratory function, but is reasonable for monitoring of patients with acute severe croup.

10.2.1.1 Future directions for research

Measurement of oesophageal pressure changes together with some measurements of air flow (either direct or indirect), could be used in a variety of other clinical conditions such as upper airway obstruction (laryngomalacia, vocal cord paralysis, subglottic stenosis, tracheal stenosis etc), lower airway obstruction of large airways (anatomical lesions in the trachea including vascular compression syndromes, external nodal compression and tracheal stenosis) and small airways (bronchiolitis) etc.

One of the major challenges in oesophageal manometry is to find ways of minimizing the "invasiveness" of the procedure. During the studies reported in this thesis, we were limited in the number of children with mild disease by the fact that we were unwilling to place naso-oesophageal / nasogastric tubes on children where this was not being done already. It was not possible to use a narrower feeding tube as the dynamics associated with a smaller feeding tube were significantly worse. Placement of very thin catheters may also be relatively difficult as thin catheters may curl up rather than passing through into the oesophagus. Certainly placement of oesophageal catheters in children without sedation would be extremely difficult.

It may be easier to perform oesophageal manometry using newer cathether tip pressure transducers although these have not always performed as well as expected (361). However these would not be part of the "routine" management as placement of nasogastric tubes is, and specialized equipment is required, while water manometry can be performed using standard equipment that is present in most intensive care units.

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10.2.2 Measurement of airflow

Measurement of airflow can be done using a simple face mask and pneumotachograph. This is however associated with some change in respiratory pattern, and requires sedation in most acutely ill children.

10.2.2.1 Future directions for research

Further studies could focus on the use of indirect measures of flow such as those achieved using respiratory inductance plethysmography.

The data suggest that measurement of air flow (and derivatives such as tidal volume) may be particularly useful in children with milder disease. In this setting development of simple non-invasive techniques which do not require application of a facemask to measure air flow would be extremely useful.

For studies of both air flow and intrathoracic pressure changes, it would be useful to combine the studies with measures of gas exchange (particularly as non-invasive techniques such as transcutaneous pCO_2 monitoring become increasingly available).

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10.2.3 Data processing

A series of computer programmes have been developed which enabled the calculation of multiple indices of respiratory function from basic digital data on air flow and pressure change. These programmes could be used in a number of settings with minimal modification and adaptation.

10.2.4 Limitations of the study

There were a number of limitations to the investigation of the methodology. There was a very small group of control subjects included (although the number was adequate to demonstrate marked differences between control and patients with croup). It was not possible to routinely do occlusion tests to confirm the adequacy of positioning of the oesophageal tube. The data suggest that inspiratory resistance

may have been raised (possibly as a result of partial airway obstruction by the nasogastric tube) by the methodology used in this study.

10.3 Mechanics of breathing in croup

The major findings of the data on mechanics of breathing in croup were that:

1) Oesophageal pressure changes in croup are markedly increased relative to normal controls.

The intrathoracic pressure changes that occur in patients with severe croup may help to explain the phenomenon of pulsus paradoxus which has been well documented as an important clinical sign in patients with acute severe croup.

The high intrathoracic pressure changes are clearly associated with marked increases in effort associated with breathing (as measured by indices such as the pressure time integral, the pressure time product and the work of breathing indices). Based on previous studies this increased effort of breathing will be associated with increased oxygen demand.

The marked intrathoracic pressure changes may be associated with changes in cardiac function, and may help to explain the development of acute pulmonary oedema following relief of airway obstruction in a number of clinical settings. It is interesting that there was a decrease in lung compliance in patients with acute severe croup in this study.

The combination of high oxygen demand for breathing, some infection throughout the lungs and possible increase in lung water associated with very large intrathoracic pressure changes, may contribute to the consistent finding in the literature of hypoxaemia in patients with acute severe croup.

2) Inspiratory flow limitation is a feature of patients with acute severe croup. The flow limitation probably occurs within the subglottis, and is

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associated with turbulent gas flow. This carries a number of related implications:

Some of the inspiratory effort expended by patients is "wasted" in the sense that the effort does not result in any increase in inspiratory flow and thus in tidal volume. This may explain why sedation in croup was associated with no evidence of deterioration (137), and possibly some clinical improvement.

Flow through the narrow subglottis in acute severe croup is both turbulent and extremely rapid. This implies that most particles in nebulized drugs are likely to deposit out of the inhaled gases as they pass through the area of turbulence. This may have implications for the delivery of therapeutic agents in patients with acute severe croup.

It may provide an explanation for some of the reported clinical improvements seen in patients with croup who have been treated with inhaled helium gas mixtures. In the presence of flow limitation due to turbulence, then reduction of gas viscosity (as happens with the addition of helium) may be associated with improvement in gas flow.

3) Expiratory glottic braking occurs commonly in patients with acute severe croup. It is not clear whether this is related to factors such as maintenance of lung volume in patients with severe croup.

4) Despite severe airway obstruction, patients with acute severe croup may maintain both normal tidal volumes and minute ventilation. This may help to explain why pCO_2 has been a poor predictor of the severity of airway obstruction in croup. It does mean that in severe croup assessment of severity of airway obstruction is impossible without a direct (or possibly an appropriate surrogate) measurement of intrathoracic pressure change.

5) Endotracheal intubation of patients with acute severe croup is followed by substantial improvement in airway obstruction. There is very limited

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evidence of severe small airways disease in a small group of children who have been intubated for acute severe croup.

The findings related to the study of the mechanics of breathing are unique, and have never been reported previously. The findings also provide a basic understanding of the pathophysiology of croup, and it may be possible to extrapolate these findings to other conditions characterized by upper airways obstruction.

10.3.1 Limitations of the study

This study has a number of limitations. There were relatively few patients admitted to the study, and particularly patients with mild disease. This was the result of a reluctance to undertake invasive studies on patients with mild croup – these children were not being sedated routinely, nor were nasogastric tubes placed routinely. Thus it is possible that the profile of airway obstruction and mechanics of breathing may be different in milder patients. In addition all these patients were sedated, although there is little evidence that the sedation would have fundamentally affected the findings regarding the mechanics of breathing.

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10.3.2 Directions for future research

It would be very useful to use the same methodology on patients with other forms of severe upper airways obstruction.

Klein and Reynolds (269) have previously reported on the results of oesophageal manometry in patients with severe oropharyngeal obstruction. In those studies they did not measure air flows, and it would be of interest to add assessement of air-flows and volumes to measurements of patients with severe oropharyngeal obstruction (although it would not be possible to measure airflows accurately in patients treated with continuous insufflation of the pharynx – as in their study). Beardsmore et al (305) have used plethysmography to describe the airways resistance in a number of infants, including 3 infants with laryngomalacia. They

demonstrated that the inspiratory resistance pattern was very similar to that of patients with croup, while (as expected) there was minimal expiratory resistance.

Newth and others (139,362) have used the rhesus monkey for experiments regarding the thoraco-abdominal phase angle changes during the imposition of a fixed inspiratory resistance. That model is more closely related to laryngomalacia (as above), and it would be interesting to examine the effects of additional inspiratory and expiratory resistance on the mechanics of breathing in these animals. It would be appropriate to use a variable inspiratory resistance (as happens with flow limitation) in this model to see whether the responses are different to those related to a fixed inspiratory resistance. This may also provide an experimental context in which the implication of the expiratory "grunting" could be examined.

Given that these studies, together with those of Jaroslawski (327) suggest that flow limitation at the larynx is related to turbulent airflow, it would be appropriate to measure the effects of helium mixtures on the mechanics of breathing in patients with croup. Measurement of airflow using this methodology may be challenging in the setting of changing gas composition, but it would be possible to measure the effort related to breathing in an objective way using oesophageal manometry. This may help to define the place (if any) of heliox mixtures in the management of severe croup (or other causes of upper airway obstruction). It would be possible to examine the effect of different gas concentrations and durations of therapy with helium.

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10.4 Effect of adrenaline nebulization

1) Some patients with acute severe croup show a dramatic improvement (of limited duration) in respiratory functions following nebulization with adrenaline. In the early literature, adrenaline nebulization was delivered by positive pressure ventilation and it is possible that attention to mode of delivery of adrenaline may also be useful.

2) Changes in respiratory function in patients with severe croup can easily be demonstrated using parameters which incorporate the intrathoracic pressure

changes. Intrathoracic pressure changes can easily be monitored in patients with croup using equipment that is readily available in any paediatric intensive care unit. The magnitude of changes in parameters related to intrathoracic pressure changes is substantially higher than changes in conventional measures such as respiratory rate and measures of flow and volume.

3) Some measures of tidal flow volume analysis (including the area within the flow-volume loop, and the time to maximum expiratory flow as a proportion of expiratory time) may be useful for the objective assessment of severity of airway obstruction in patients with acute severe croup. However although there are substantial differences in these measurements between croup and control patients, the measures appear to be less sensitive in differentiating between patients of varying severity of illness.

10.4.1 Directions for future research

Oesophageal manometry can be used to assess the response of patients with severe upper airways response to therapy. As one example, it is not clear why some patients do not improve following adrenaline nebulization, and further studies will be required to optimize the dose, mode of administration and dose frequency of adrenaline in patients with acute severe croup.

Previously Steele et al (118,144) have demonstrated that it is possible to monitor pulsus paradoxus non-invasively, and that there was a positive correlation between pulsus paradoxus and clinical score. It would be useful to measure oesophageal manometry together with the non-invasive pulsus paradoxus and assess the correlation, and the contribution that the magnitude of the pulsus paradoxus can make to clinical assessment.

Unfortunately application of a facemask is not well tolerated without sedation in patients with acute severe croup. Indirect measurements of tidal breathing flow and volumes such as those derived from respiratory inductance plethysmography may provide a non-invasive way of obtaining these measurements. It seems that

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measurement of tidal flow volume parameters may be useful in assessment of patients with milder croup. It would be important to measure oesophageal manometry in these patients together with the tidal flow volume analysis until the relationships between the measurements have been established. Doing these measurements in patients who are receiving therapy such as adrenaline nebulizations may create a useful clinical setting as there are clearly patients who change their respiratory mechanics in response to adrenaline and thus provide an opportunity of evaluate the capacity of a particular method to describe change.

10.5 Clinical scores in the assessment of severity of croup

1) A wide variety of clinical scoring systems have been developed and used in research studies (it is difficult to know how many are routinely used in clinical practice). Most scores are numeric and it is not always clear as to whether particular thresholds are established for intervention related to those scores. The Klein score is linked to a particular intervention (prolonged grade 3 croup is associated with the recommendation for endotracheal intubation). Despite the plethora of clinical scores available, there is extremely limited data confirming the accuracy, reproducibility and reliability of these scores.

2) Many of the clinical features used in clinical scoring systems are unlikely to be useful measures of the severity of airway obstruction.

3) Clinical signs that are related to intrathoracic pressure changes (retraction and pulsus paradoxus) may be worth further evaluation. Pulsus paradoxus has been shown to be related to severe croup, although there is not enough evidence available as to whether pulsus paradoxus may disappear with fatigue (as has been suggested in severe asthma).

10.5.1 Future directions in research

There is a need to consider the particular reasons for the use of clinical scores in croup. If they are to be used to identify the appropriateness of a particular clinical

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response, then they need to be evaluated against their accuracy and reproducibility in predicting that response. Ideally the score should be calibrated in such a way that all children who require intubation are correctly identified by the score, while relatively few children are unnecessarily intubated. The data presented in this thesis suggests that most patients with severe airway obstruction are identified by a croup score of 3, but that there is wide variability in the severity of airway obstruction within that group of children. It would be very useful to review the data from the Red Cross War Memorial Children's hospital (where the score together with related management plan has been in routine use for > 20 years). An underlying question would be whether there were unexpected collapses or deteriorations in children who had scores of <3. Similar studies are required to address the question of whether particular scores can predict that it is safe to send a children with croup home.

As the Westley score is the most commonly used clinical score and it forms the basis of a range of other clinical scores, it would be useful to compare the Westley score with objective measures of both air flow (and related measures) and oesophageal pressure changes in patients with croup over a wide range of clinical severity. This will almost certainly need to be done as a multicentre study in order to get adequate numbers of subjects

A feature of many of the clinical scores is that they utilize clinical signs and symptoms that are poorly defined or which have poor inter-observer reliability. A focus of clinical score development, is the identification of clearly defined clinical signs that can be used reliably by a range of observers, and which relate well to objective measures. Ideally the number of parameters used in a score should be as small as possible. The data also suggests that while some signs may be useful in mild croup, other clinical signs may be more useful in more severe croup and vice versa.

Studies of steroid therapy made considerable use of croup scores that have clearly been inadequately validated. The longer term experience of a reduction in severe croup related to use of steroids suggests that the conclusions of the studies were not incorrect. However this study has shown that in the future development and validation of clinical scores, for research purposes, careful validation against some

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objective measures of disease severity may be useful. This will however be complex as scores (and objective measures) that are effective over a certain range of disease may not be effective or valid over the whole range of severity. This means that validation processes must include an adequate range of patients, and objective measures must also be assessed over an adequate range of disease severity.

10.6 Comparison of clinical scores with objective data

Changes from grade 2 to 3 in the Klein croup score are associated with more severe airways obstruction. However there is overlap in airways resistance between the grades, and changes in airways resistance (following nebulization) are not always reflected by changes in the croup score.

Within the group of patients assessed as having a grade of 3 in the Klein score there is a wide range of severity of airway obstruction.

10.6.1 Limitations of the study

A major limitation of the study is that more commonly used clinical scores such as the Wesley score were not evaluated. In addition there were few "mild" patients admitted into this study, and it was not possible to fully evaluate the clinical score across the full spectrum of clinical severity of illness.

10.6.2 Future directions in research

A particular challenge in the relationship between clinical scores and objective data is developing a sense of cut-off points that are clinically significant.

In milder croup assessment of air flow and tidal volumes may be a useful assessment of the severity of croup. It may be useful to use non-invasive measures of air movement in patients with milder croup in comparision with a variety of clinical measurements

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Intrathoracic pressures changes do relate to the severity of airways obstruction. The magnitude of those pressure changes relate to additional factors such as the age, size and strength of the individual child. However the current data do not allow us to determine a particular numeric value when intervention is required. Given that oesophageal manometry can be used relatively easily in sick children in the PICU environment, it would be useful to collect data on all children admitted to PICU with severe croup and to compare that data with the perceived need for clinical intervention. The data shown in this thesis suggests that in the PICU environment it would be adequate to measure oesophageal pressure change and the pressure rate product without the challenges associated with the measurement of air flow. It would certainly be more feasible to collect data from more patients using a simpler technique. It is unlikely that single centres would be able to collect data on enough patients in the current era, and multicentre studies would be required to collect enough data.

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10.7 Finally

Studies on patients with acute severe croup, using oesophageal manometry and measurement of airflow at the mouth have provided unique insights into the mechanics of breathing of patients with severe croup. Those insights may help to explain some of the clinical features that have previously been noted in patients with croup. In addition we have demonstrated that simple technology that is generally available in paediatric intensive care units across the world could be used to evaluate the severity of airways obstruction in croup (and in other causes of upper airways obstruction).

An evaluation of clinical scoring systems that have been reported for use in croup has demonstrated that there are many clinical features included into those scores that are poorly defined, cannot be recorded consistently by a range of observers and in many cases are unlikely to be related to the severity of airways obstruction in croup. Furthermore very few of the reported clinical scores have been evaluated comprehensively for clinical (or research use). Many of the clinical studies of croup utilize these scores, and there are concerns as to whether these scores can be regarded as appropriate endpoints for clinical evaluation of therapy.

An understanding of the mechanics of breathing in croup may help in the development of future clinical scores, and objective measures of airway obstruction should be included in the comprehensive evaluation of complete scores in the future.

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Appendix 1:

Klein Score

GRADE	CLINICAL FEATURE
1	**Inspiratory obstruction* only at rest**
2	**Inspiratory and expiratory obstruction+ at rest**
3	**Inspiratory and expiratory obstruction at rest plus palpable pulsus paradoxus *or* active abdominal contraction during expiration ¶**
4	**Marked retractions, apathy, cyanosis ¶**

* Signs of inspiratory obstruction are: Inspiratory stridor, prolonged inspiration, retractions and tracheal tug

\+ Prolonged expiration is the major sign of expiratory laryngeal obstruction.

¶ Lack of response to therapy at Grade 3 or assessment at Grade 4 requires intubation.

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Appendix 2
Assessment of measurement system

Appendix 2.1 Pressure measurement

Oesophageal pressure change with tidal breathing (ΔPoes) was measured with a pressure transducer (1290A, Hewlett-Packard, Waltham, MA, USA) coupled to a water-filled 8 French (1.0 mm internal diameter) vinyl plastic feeding tube. Signals from the transducer were recorded using a a polygraph (775B Hewlett-Packard, Palo Alto, CA, USA) on heat sensitive paper.

Airway pressure changes were measured using the same pressure transducer connected to the facemask via a 4mm rigid plastic tube.

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2.1.1 Steady state response

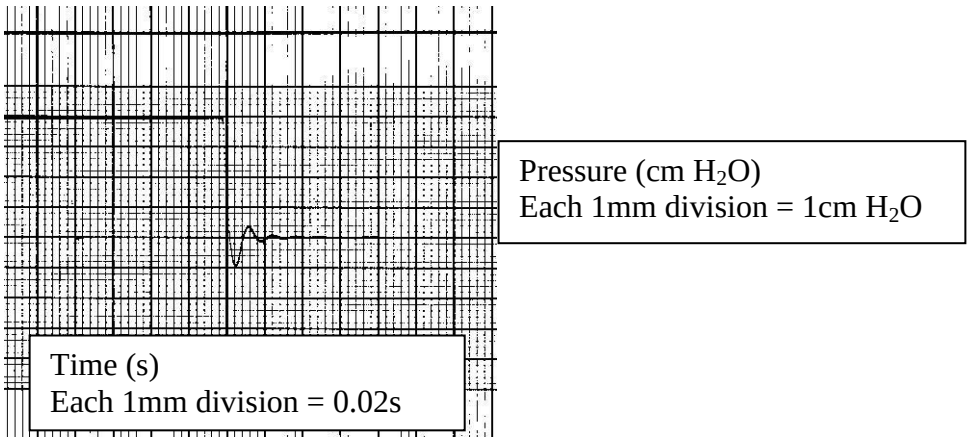
The steady state response of the manometer system was assessed by applying static pressures to a chamber over the range 0-100cm H_2O. The response for the systems was linear over that range.

2.1.2 Frequency response

A glass chamber was half filled with water, and the oesophageal tube was inserted into the chamber under the water level. The chamber was sealed using a condom, and the pressure was raised to 20cm H_2O by air inflation. A step response was placed onto the system by bursting the condom with the touch of a heated soldering iron. Amplified traces were recorded

The frequency response of the system was assessed from the step response (362) (see figure A 2.1 and Table A 2.1) and was linear to 9Hz for the oesophageal manometry system and to 80hz for the airway manometry system.

Figure A 2.1: Step response



This figure illustrates the step response of a 8FG feeding tube connected directly to the transducer and inserted into a pressure chamber. A pressure of 20cm H_2O had been applied within the chamber, and a step response was initiated by touching the condom (which closed the chamber) with a hot soldering iron. The signal had been amplified and then recorded onto heat sensitive paper running at 50mm / s.

Alternatively the responses of the oesophageal manometry system were assessed using a sine wave-form over a range of frequencies. The tip of the oesophageal catheter was placed inside a water-filled pressure chamber. Sine wave-forms over a range of frequencies were generated in the chamber by driving a piston with a Hwelett Packard 3314A function generator. Traces from a Honeywell MTC p5f catheter tip transducer (frequency response > 20kHz) were used to confirm that the pressure swings within the chamber were as expected.

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Table A 2.1. Data from a step response

(Calculated as per Fry D.L. 1960)

Test	x1	x2	X2/X1	Ln2	h	Time (s)	Damped Frequency (Hz)	Undamped Frequency (Hz)	Linear Range (Hz)
1	21	10.5	0.500	0.480	0.215	0.073	13.793	14.125	9.181
2	21.5	9.5	0.195	2.668	0.461	0.073	13.793	15.546	10.105
3	20.5	9.5	0.215	2.366	0.440	0.070	14.286	15.906	10.339
4	20	10	0.250	1.922	0.404	0.073	13.793	15.076	9.800
Mean								**15.163**	**9.856**
Standard deviation								**0.668**	**0.434**

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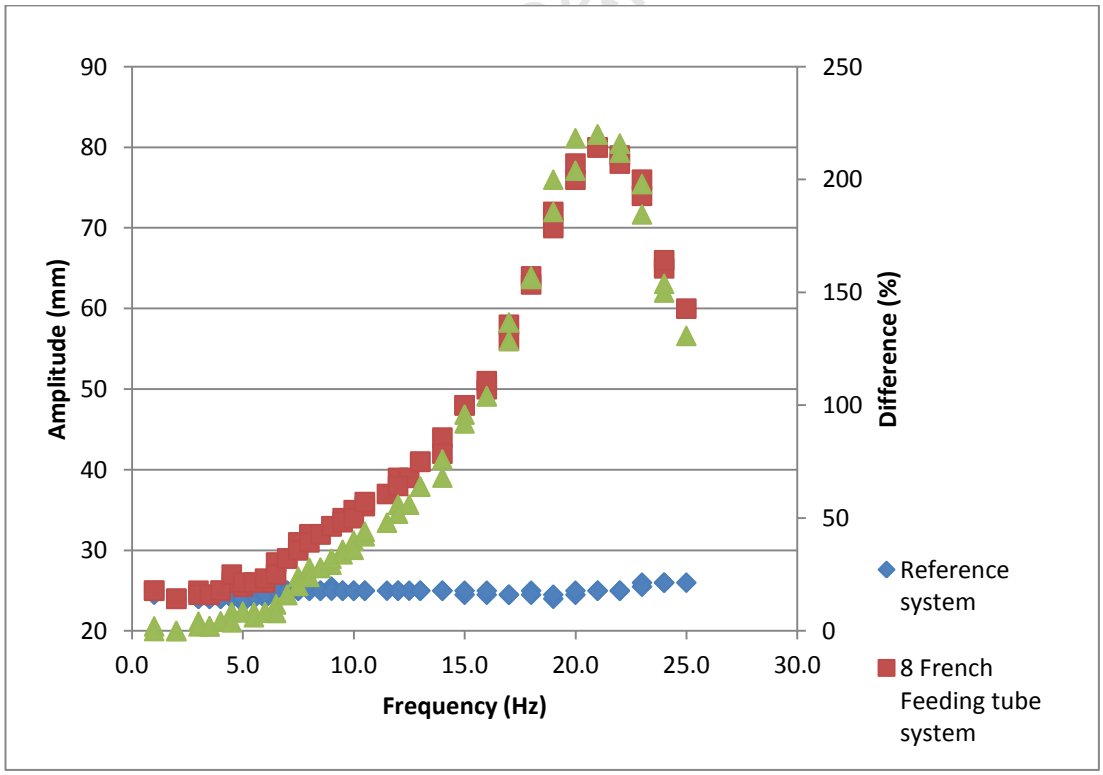
Figure A 2.2: the Effect of frequency on amplitude



In this graph the amplitude of the signal for the reference and oesophageal manometry systems are plotted over a range of frequencies. The green data represents the difference between the 2 signals as a percentage of the reference signal.

As shown in figure A 2.2, the oesophageal pressure recording system had a resonance frequency of 21 Hz and a linear amplitude response (<10% deviation from baseline) in the range of 0-6 Hz.

Appendix 2.2 Flow measurement

Flow was measured with a differential pressure transducer (Sanborn 270, Hewlett-Packard, Waltham, MA, USA) and heated pneumotachograph (Fleisch 0, resistance 5 cm H_2O/L/s at 0.2 L/s) coupled to a facemask (Vital Signs, #2, Totawa, NJ, USA) or directly to the endotracheal tube of intubated patients. The response of the pneumotachograph and transducer was linear in the range 0 - 0.2 L/s and 1-10 Hz. Prior to each study the pneumotachograph was calibrated against flow as measured using a rotameter.

Flow signals, oesophageal pressures (Poes) and peak-to-trough changes (ΔPoes) were recorded with a polygraph (775B Hewlett-Packard, Palo Alto, CA, USA) on heat sensitive paper at 25 or 50 mm/s.

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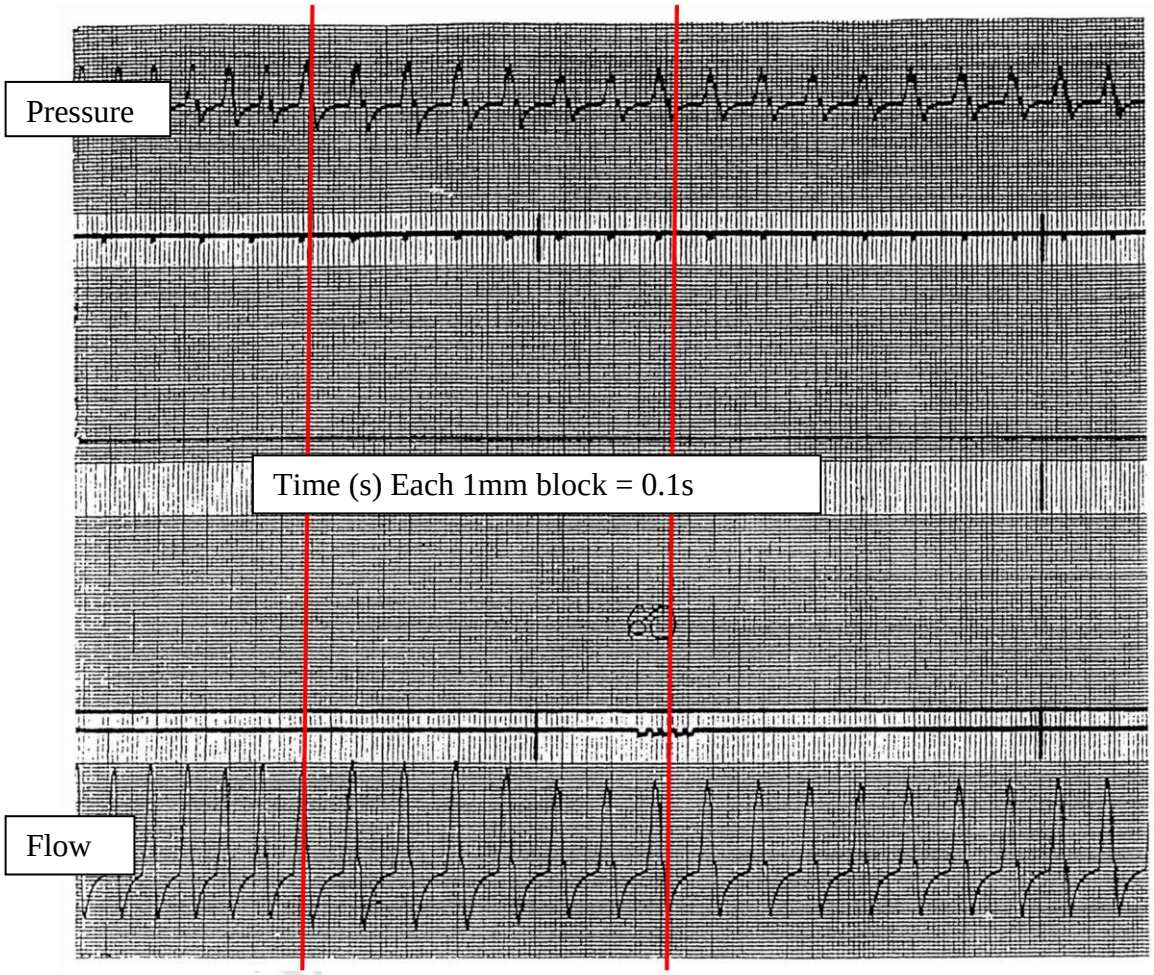
2.2.1 Frequency response vs pressure measurement system

An anaesthetic bag was placed inside a Perspex box. The bag was connected to a Siemens Servo 900 ventilator which could be cycled at a range of respiratory rates, pressures and volumes

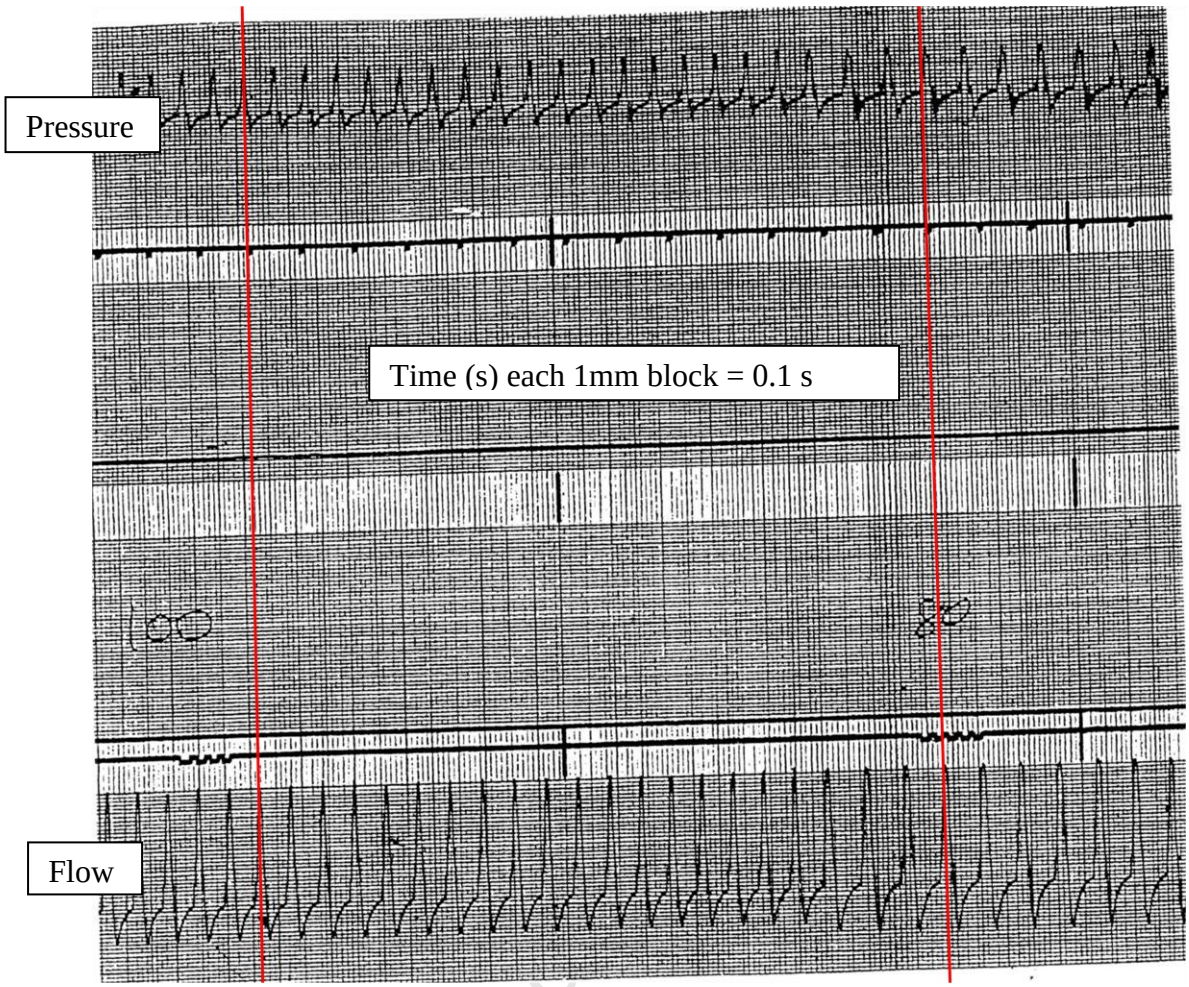
The pneumotachograph and differential pressure transducer system was connected to a port on the sealed Perspex box. A water-filled 8 French (1.0 mm internal diameter) vinyl plastic feeding tube was inserted through another port into the same Perspex box and coupled to a pressure transducer (1290A, Hewlett-Packard, Waltham, MA, USA). This meant that pressure waves applied to the anaesthetic bag would be applied to the flow and pressure systems simultaneously. The ventilator was then cycled at a range of frequencies up to 120 breaths per minute, and output from both the flow and pressure systems was processed through a polygraph (775B Hewlett-Packard, Palo Alto, CA, USA) on heat sensitive paper.

Output from the studies is shown in figure A 2.3.

Figure A 2.3: Comparision of flow and pressure responses



This figure shows the output from the "bag in a box" experiment with flow and pressure traces with a rate of 60 cycles / min with paper running at 10mm/s. The red lines have been aligned with the axis of the paper and show that there is minimal phase difference between the pressure and flow traces (both with the peaks and with the troughs).



This trace shows the same experiment with the frequency at 100 breaths/min on the left and at 80 b/min on the right. The red lines have been aligned with the axis of the paper and show that there is minimal phase difference between the pressure and flow traces.

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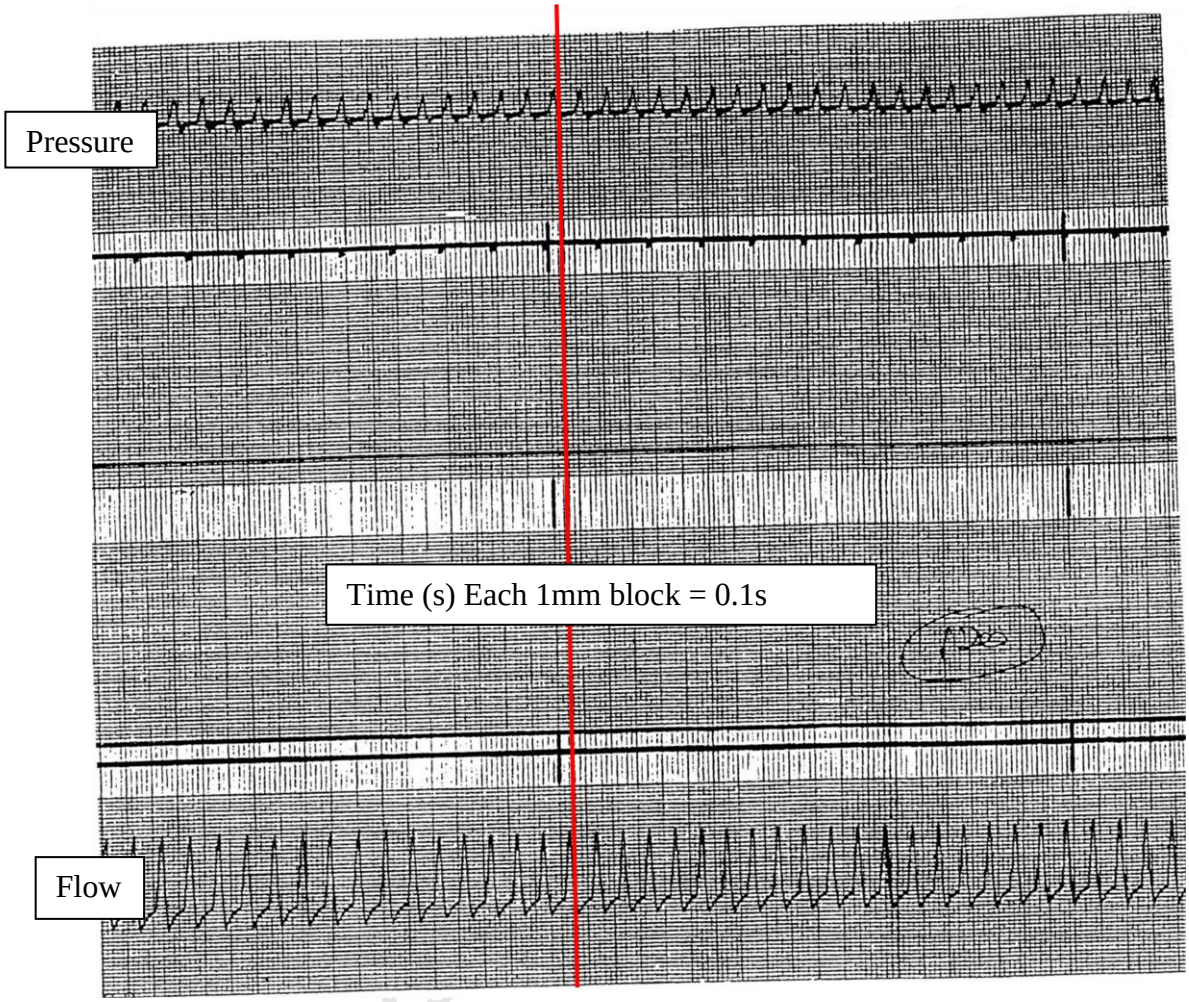

This figure shows the same experiment with a frequency of 120 b/min. the red line is aligned with the axis of the paper to show that there is minimal phase lag at this frequency.

Appendix 3
Description of Data processing

Appendix 3.1 Digitization of data

Representative samples of three to ten breath sequences showing minimal breath-to-breath variation in pressure and flow were selected by inspection and entered into a personal computer by manually tracing the individual flow and pressure graphs on a digitizer board (Summasketch Plus, Summagraphics, Fairfield, CT, USA), and analyzed using custom-written computer programs. The starting point for each trace was selected at a point of zero flow

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Table A3.11: Programmes utilized to process data

Program	Function	Input data	Process	Output process
	Digiti-zation of trace	Data from Summasketch Digitizer Board	Checked alignment of paper on board.	Recorded baseline data (regarding the alignment of the trace). Recorded data from digitizer at every point where moved more than 0.025 mm in x or y plane. Written to file as stream of x and y co-ordinates separately for flow and pressure. File labeled as "name"."trace number
Barop2.exe	Correction of	File labeled as "name"."trace	Collected information	Output to file: "name"."trace

Program	Function	Input data	Process	Output process
	digitized points into flow and pressure traces. Calculation of volume and elastic pressure	number	from operator regarding paper speed, scales of pressure and flow traces, orientation (upwards or downwards of flow data). Interpolated flow and pressure data at 0.5mm. Rotated flow and pressure data to correct for orientation of paper. If points of zero flow were not indicated, then data was interpolated for those points. Data were written to file.	number”“d”. Data in columns with time, flow, pressure, elastic pressure, volume.
newcalr4.exe	Correction of volume trace for drift using	Data from file ”name”.”trace number””d” from time,	Flow data was integrated to provide volume data.	Output to file entitled “name”. “trace number”r. Also created file name

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Program	**Function**	**Input data**	**Process**	**Output process**
	least mean squares analysis. Calculation of resistance data	flow and pressure data columns	Drift of the volume signal was calculated using a least mean squares analysis and the drift was corrected. Also calculated elastic recoil pressure (from pressure at points of zero flow and assuming linear change with volume), airways resistance and total resistance	Fileinfo with names for all outputs for further processing of this trace
Newbper. exe	Programme to interpolate several breaths for volume based on percent of tidal volume.	read data from .r	corrected volume for drift, converted volume to % tidal volume and interpolated at 5% intervals. This version includes the additional	Output to file entitled "name". "trace number"p

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Program	**Function**	**Input data**	**Process**	**Output process**
			resistance data	
Newavol3 .exe	Averaging of several breaths	read data from .r		Output to file entitled “name” “trace number”.pav
Newasum 2.exe	Average of several breaths	reads the data from .*p	Averages data over several breaths at points of 25% increments in tidal volume. This version includes resistance (not corrected for compliance	Output to file entitled “name” “trace number”.sum and .pav
Avework4	Calculations of work and effort of breathing	* Reads .r and	uses volume and pressure to calculate the resistive work of breathing, and pressure and time to calculate the pressure time integral. This version separates inspiratory and expiratory ptint	outputs to vol (appending the data)
newctim	Programme to	Reads from .r	Marks the start of each breath	Writes IE data, compliance data to

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Program	Function	Input data	Process	Output process
	correct time base (so each breath starts from time zero, assess Inspiratory / Expiratory ratio and calculated dynamic compliance		and recalculates the time base so that each breath starts at time zero. Calculates IE ratios. Calculates compliance on each breath	.vol
Newfv3	Programme to calculate flow volume parameters for several breaths	from the .r file input	this version read files containing the resistance not corrected for elastic recoid pressure * */	output is to .*vol

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Appendix 3. 2 Calculation of derived indices

Appendix 3.2.1 Flow data

Flow data was obtained directly from the traces.

Appendix 3.2.1.1 Volume

Volume was calculated by integration of the flow trace over time (using the programme newcalr4.exe). Drift was calculated and corrected for using a least mean squares analysis of the recorded breaths.

Tidal volume was calculated as the volume inspired from points of zero flow indicating end expiration using the programme newavol3.exe. Data was expressed both as ml and as ml/kg (these corrections were made after data had been loaded into a spreadsheet such as Excel).

Minute ventilation was calculated from the product of tidal volume and respiratory rate using Microsoft Excel and expressed as ml/min or ml/min/kg.

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Appendix 3.2.1.2 Peak inspiratory and expiratory flow

Other parameters derived from the flow data included peak (newavol3.exe) and mid-inspiratory flow rates (newasum2.exe), and peak (newavol3.exe) and mid-expiratory flow rates (newasum2.exe).

Appendix 3.2.1.3 Time and volume related to points of peak inspiratory and expiratory flow

The parameters time to peak inspiratory flow as fraction of inspiratory time (Tmif / Ti_{TOT} (%)), time to peak expiratory flow as fraction of expiratory time (Tmef / Te_{TOT} (%)), inspiratory volume at peak inspiratory flow as fraction of inspiratory tidal volume and expiratory volume at peak expiratory flow as fraction of expiratory tidal volume were calculated using the programme newfv3.exe (see appendix 2).

Appendix 3.2.1.4 Flow at 25, 50 and 75% of tidal volume

Flow at quartile points of tidal volume were calculated using the programme newavesum2.exe (see appendix 2). The tidal volume of each breath was calculated, and this was then divided into quartiles. The flow data at each quartile point was recorded, or if there was not data available at that volume point, data was calculated by interpolation from data points to either side of that point.

Appendix 3.2.1.5 Area within the flow-volume curve

The area within the flow volume curve for each breath was calculated using the programme newfv3.exe (see appendix 2) by means of integration.

Appendix 3.2.2 Pressure data

Appendix 3.2.2.1 Peak Pressure values

Peak inspiratory and expiratory pressure values were identified and averaged using the programme newavol3.exe (see appendix 2). This programme identified the peak pressure change during inspiration and expiration. No correction was made for pressure change from point of zero flow.

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Appendix 3.2.2.2 Pressure Time Integral

The pressure time integral was calculated from integration of the area under the pressure time curve using the programme avework4.exe (see appendix 2).

The integral was calculated for each breath, averaged over the period of the trace and then multiplied by the respiratory rate to provide a pressure time integral per minute.

Appendix 3.2.2.3 Pressure Time Product

The Pressure Rate Product was calculated from the product of the respiratory rate and the average peak to peak oesophageal pressure change per breath (prior to the application of the facemask. These calculations were performed on data obtained

during facemask application using the programme avework4.exe (see appendix 2), and manually prior to application .of the facemask.

Appendix 3.2.3 Interrelationship between flow and pressure derived data

Appendix 3.2.3.1 Dynamic Compliance

Compliance was calculated from the volume and pressure data. The compliance was calculated as the inspiratory tidal volume (i.e. the volume change from the point of zero flow at the end of expiration) divided by the pressure difference between the points of end-expiration and end-inspiration as marked by points of zero flow.

Appendix 3.2.3.1 Resistance

Pulmonary resistance was calculated for each time point (newcalr4.exe) using the formula R= Pres/F; where R is resistance, F is flow and Pres is calculated from ΔP - Pcl. Pcl (calculated from oesophageal ΔP at points of zero flow and assuming linear relationship of elastic recoil pressure with volume over a tidal breath at the time of calculation. The operator discarded artefactual results calculated around points of zero flow.

Total resistance was calculated for each time point using the formula R=ΔP/flow where ΔP = the oesophageal pressure change at that time and flow is the flow at the mouth at that time point.

Appendix 3.2.3.2 Work of breathing

Work of breathing (WR) was calculated as the area within the pressure volume curve. This was calculated using programme avework5.exe which integrated the area within the pressure volume curve. This was corrected for the weight of the patient.

The rate of work of breathing was calculated as the product of the work of breathing and the respiratory rate

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Appendix 3.2.3.4 Volume for effort

Volume for effort was calculated from the ratio of minute ventilation (ml/min/kg) to pressure time integral (cm H2O.s/min). This calculation was performed on derived data using Microsoft Excel

Appendix 3.2.3.5 Flow pressure curves

In order to produce plots of flow vs. pressure, data derived from the digitized traces was interpolated to provide data at intervals of 1ml or 5% of tidal volume (newbper1.exe and newasum2.exe).

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Appendix 4: Programmes for data pro

Appendix 4.1 Programme to process digitized data(barop2)

(This was called barop2.exe)

```
Program fixit; {to reorder the numbers as input from the digitizer}
{this version does not attempt to correct the flow for  barometric temperature and
pressure, nor does it calculate the elastic recoil pressure or volume}
const
Array_max = 1300;
XINC = 0.5;
bufname : string[8] = 'fileinfo';
d : string[1] = 'd';
ave : string[1] = 'a';
vv : string[1] ='v';
r : string[1] = 'r';
per : string[1] = 'p';

type
  TyI   = integer;
  TyS20 = string[20];
  Data_Array = array[1..Array_Max,1..2] of real;
  base_array = array[1..4,1..2] of real;
  Ifile = text;

var
  Base_Acceptable : boolean;
  c : char;
  infilename, avefilename, volfilename, rfilename, percfilename,
  outfilename : TyS20;
  f : data_array;
```

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```
  p : data_array;
  v : data_array;
  ep : data_array;
  base_data1 : base_array;
  outfile : Ifile;
  base1file : Ifile;
  infile : Ifile;
  buf : Ifile;
  cnt1,
  cnter_f,
  cnter_vol,
  cnter_p,
  cnter_ep : TyI;
  INT, sf, sp, ps : real;
{
**************************************************************************
**** }
procedure Get_File_Names;
begin
      writeln('PLEASE ENTER NAME OF INPUT FILE TO BE READ');
      readln(Infilename);
      outfilename := concat(infilename, d);
      rfilename := concat(infilename, r);
      volfilename := concat(infilename, vv);
      avefilename := concat(infilename, ave);
      percfilename := concat(infilename, per);
      writeln;
      writeln ('THE FILES ARE BEING ACCESSED');
      assign(buf, bufname);
      rewrite(buf);
      writeln(buf, infilename);
      writeln(buf, outfilename);
      writeln(buf, rfilename);
      writeln(buf, avefilename);
```

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```
      writeln(buf, volfilename);
      writeln(buf, percfilename);
      close(buf);
end;
{
**************************************************************************
**** }
procedure Error_Trap1;
begin
   Writeln('ERROR - MISSING CO-ORDINATE');
end;
{
**************************************************************************
**** }
procedure Error_Trap2;
begin
   Writeln('ERROR - TOO MANY FLOW POINTS');
end;
{
**************************************************************************
**** }
procedure Error_Trap3;
begin
   Writeln('ERROR - TOO MANY PRESSURE POINTS READ');
end;
{
**************************************************************************
**** }
Procedure Fill_in_c;

var
p0,
mark,
base,
```

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```
I0 : TyI;
sign : real;

begin
    p0 := 0;
    Cnt1 := 1;
    cnter_f := 1;
    cnter_p := 1;
    sign := 1.0;
    mark := 0;
    I0 := 1;
    assign(infile, infilename);
    reset(infile);
    while not EOF(infile) do begin
    read(infile,c);
     case c of
          ':' : mark := mark + 1;
          'A'..'Z' : p0 := 0;
          '-' : sign := -1.0;
          '0'..'9' : p0 := p0 * 10 + integer(c) - 48;
          ',' : begin
                if mark = 1 then begin
                  base_data1[cnt1,I0] := (sign * p0)/40.0;
                  p0 := 0;
                  sign := 1.0;
                  If I0 = 2 then I0 := 1 else I0 := 2;
                  If I0 = 1 then cnt1 := cnt1 + 1;
                end;
                 if mark = 2 then begin
                f[cnter_f,I0] := (sign * p0)/40.0;
                p0 := 0;
                sign := 1.0;
                  If I0 = 2 then I0 := 1 else I0 := 2;
                  If I0 = 1 then cnter_f := cnter_f + 1;
```

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```
                    if cnter_f > array_max then error_trap2;
                    end;
                     if mark = 3 then begin
                  p[cnter_p,I0] := (sign * p0)/40.0;
                  p0 := 0;
                  sign := 1.0;
                    If I0 = 2 then I0 := 1 else I0 := 2;
                    If I0 = 1 then cnter_p := cnter_p + 1;
                    if cnter_p > array_max then error_trap3;
                    end;
               end;
               end;
          end;
     writeln('cnter_f is:',cnter_f);
     writeln('cnter_p is:',cnter_p);
     writeln;
     end;
{
**********************************************************************
**** }
Procedure Clear_arrays (var Work_array : data_array);

var
i0,
num : TyI;

begin
    i0 := 1;
    num := 1;
    for num := 1 to array_max do begin
       for i0 := 1 to 2 do begin
       work_array[num,i0] := 0;
end;
end;
```

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```
end;
{
**************************************************************************
**** }
procedure Zero_Numbers (var Work_Array : Data_Array; var Cnt : TyI);

var
I0 : TyI;
p,
q : Real;

begin    {procedure to zero the numbers}
        I0 := 1;
        p := Work_Array[1,1];
        q := Work_Array[1,2];
        while I0 <= cnt do
         begin
            Work_Array[I0,1] := Work_Array[I0,1] - p;
            Work_Array[I0,2] := Work_Array[I0,2] - q;
             I0 := I0 +1;
         end;
end;
{
**************************************************************************
**** }
procedure Zero_base (var Work_Array : base_Array; var Cnt : TyI);

var
I0 : TyI;
p,
q : Real;

begin    {procedure to zero the numbers}
        I0 := 1;
```

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```
        p := Work_Array[1,1];
        q := Work_Array[1,2];
        while I0 <= cnt do
         begin
            Work_Array[I0,1] := Work_Array[I0,1] - p;
            Work_Array[I0,2] := Work_Array[I0,2] - q;
             I0 := I0 +1;
         end;
end;
{
**********************************************************************
**** }
procedure Rotate_Data (var Work_Array : Data_Array; cnt : TyI);
var
  a,
  u,v,w,z,
  r : real;
  i0 : TyI;

begin
a := 0;
r := 0;
r := Base_Data1[2,2] / Base_Data1[2,1];
Writeln('TAN OF ANGLE OF ROTATION IS:',r);
a := ArcTan(r);
Writeln('ANGLE OF ROTATION IS',a);
i0 := 1;
   while i0 <= cnt do
  begin
    v := Work_array[i0,1];
    u := Work_array[i0,2];
    w := v * cos(a) + u * sin(a);
    z := u * cos(a) - v * sin(a);
    Work_array[i0,1] := w;
```

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```
   Work_Array[i0,2] := z;
   i0 := i0 +1;
 end;

end;
{
*************************************************************************
**** }
Procedure interpolate_zero_points (var cnt : TyI);

var
  work_arrayf,
  work_arrayp : data_array;
  y,i0,m : TyI;

begin
   i0 := 1 ;
   y := 1;
   while i0 < cnt do begin
       if (f[i0,2]*f[i0+1,2]) < 0 then begin
          work_arrayf[y,1] := f[i0,1];
          work_arrayf[y,2] := f[i0,2];
          work_arrayf[y+1,2] := 0;
          work_arrayf[y+1,1] := f[i0,1] + ( (f[i0+1,1] - f[i0,1]) *
                    abs(f[i0,2] / (f[i0 + 1,2] - f[i0,2])) );
          work_arrayp[y,1] := p[i0,1];
          work_arrayp[y,2] := p[i0,2];
          work_arrayp[y+1,1] := work_arrayf[y+1,1];
          work_arrayp[y+1,2] := work_arrayp[y,2] + (((p[i0+1,2] - p[i0,2]) *
                    (work_arrayp[y+1,1] - work_arrayp[y,1])) /
                    (p[i0+1,1] - p[i0,1]));
          y := y + 2;
          i0 := i0 +1;
          end
```

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```
            else begin
            work_arrayf[y,1] := f[i0,1];
            work_arrayf[y,2] := f[i0,2];
            work_arrayp[y,1] := p[i0,1];
            work_arrayp[y,2] := p[i0,2];
            i0 := i0 + 1;
            y := y + 1;
          end;
         end;
    m := 1;
    while m < i0 do begin
      f[m,1] := work_arrayf[m,1];
      f[m,2] := work_arrayf[m,2];
      p[m,1] := work_arrayp[m,1];
      p[m,2] := work_arrayp[m,2];
      m := m + 1;
      end;
    end;
{
*************************************************************************
**** }
Procedure Correct_the_flow;

var
  m : TyI;
  cnt_c : TyI;

begin
    writeln('IF INSPIRATORY FLOW POSITIVE THEN m=1');
    writeln('IF INSPIRATORY FLOW NEGATIVE THEN m=2');
    writeln('PLEASE ENTER CORRECT VALUE FOR m');
    readln(m);
    cnt_c := 1;
    while cnt_c < cnter_f do begin
```

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```
        if m = 1 then begin
          if f[cnt_c,2] < 0 then begin
            f[cnt_c,2] := f[cnt_c,2] * ((760-25)/(273+22))*
                    ((273+37)/(760-47));
            end;
            end;
         if m = 2 then begin
           if f[cnt_c,2] > 0 then begin
             f[cnt_c,2] := f[cnt_c,2] * ((760-25)/(273+22))*
                    ((273+37)/(760-47));
             end;
           end;
        cnt_c := cnt_c + 1;
    end;
end;
{
*************************************************************************
**** }
Procedure calculate_elastic_pressure;

var
  el,
  i0,
  cnter,
  cnt_el,
  pr : TyI;
  work_array : Data_array;

begin          {This is to mark points of zero flow}
    i0 := 1;
    el := 1;
    while i0 < cnter_f do begin
      if f[i0,2] = 0 then begin
        work_array[el,1] := p[i0,1];
```

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```
        work_array[el,2] := p[i0,2];
        el := el + 1;
        i0 := i0 + 1;
        end
        else i0 := i0 + 1;
    end;
    cnt_el := el;
    if cnter_f < cnter_p then
      cnter := cnter_f
      else cnter := cnter_p;
    i0 := 1;
    cnter_ep := 1;
    el := 1;
    while cnter_ep <= cnter do begin
      if p[i0,2] = work_array[el+1,2] then  begin
        ep[cnter_ep,1] := p[i0,1];
        ep[cnter_ep,2] := p[i0,2];
        cnter_ep := cnter_ep + 1;
        i0 := i0 + 1;
        el := el + 1;
        end
        else begin
          if el < cnt_el then begin
          ep[cnter_ep,1] := p[i0,1];
          ep[cnter_ep,2] := work_array[el,2] + (work_array[el+1,2] -
                  work_array[el,2]) * (ep[cnter_ep,1] - work_array[el,1])
                  / (work_array[el+1,1] - work_array[el,1]);
{           writeln(ep[cnter_ep,1]:8:3, ep[cnter_ep,2]:8:3);}
          cnter_ep := cnter_ep + 1;
          i0 := i0 + 1;
        end;
       end;
    end;
end;
```

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```
{
**********************************************************************
**** }
Procedure Interpolate_The_Data(var Work_Array : Data_Array;
                               var cnt : TyI);

var
inew, i, new : TyI;
a,b,c,d,e,f : Real;
new_array : data_array;

begin
{     writeln('PLEASE ENTER DIGITIZING INTERVAL IN MM*0.1');
    readln(INT);                                    }
    INT := 0.5;   {digitizing interval set to 0.5mm}
    new := 1;
    new_array[new,1] := work_array[1,1];
    new_array[new,2] := work_array[1,2];
    i := 1;
    While i < cnt do
       begin
         if (Work_Array[i+1, 1] > (new_array[new,1] + INT)) then
         begin  { found a point that crosses x boundary }
          new_array[new+1,1] := new_array[new,1] + INT;
          new_array[new+1,2] := new_array[new,2] + ((work_array[i+1,2] -
                              new_array[new,2]) * (new_array[new+1,1] -
                              new_array[new,1]) /
                               (Work_Array[i+1,1] - new_array[new,1]));
                              { ratio of y increment }
          new := new + 1;
         end;
         if (Work_Array[i+1, 1] = new_array[new,1] + INT) then
         begin
          new_array[new+1,1] := new_array[new,1] + INT;
```

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```
            new_array[new+1,2] := work_array[i+1,2];
            new := new + 1;
          end;
          if (Work_Array[i+1, 1] < new_array[new,1] + INT) then
          i := i + 1;
        end;
   inew := 1;
   while inew < new - 1 do begin
      work_array[inew,1] := new_array[inew,1];
      work_array[inew,2] := new_array[inew,2];
{       writeln(work_array[inew,1]:8:3, work_array[inew,2]:8:3);  }
      inew := inew + 1;
    end;
   cnt := inew - 1;
end;
{
*************************************************************************
**** }
procedure Check_Base;
var
Xlimit : real;
Ylimit : real;
a : real;

begin
    Xlimit := 2.5;
    Ylimit := 2.5;

    Base_acceptable := true;
    If Abs(Base_Data1[1,1] - Base_Data1[3,1]) > Xlimit then
        Base_Acceptable := false;
    If Abs(Base_Data1[1,2] - Base_Data1[3,2]) > Ylimit then
        Base_Acceptable := false;
    If Abs(Base_Data1[2,1] - Base_Data1[4,1]) > XLimit then
```

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```
        Base_Acceptable := false;
    If Abs(Base_Data1[2,2] - Base_Data1[4,2]) > YLimit then
        Base_Acceptable := false;

end;
{
**********************************************************************
**** }
Procedure Calc_volume (var calc_array : data_array;
                var new_array : data_array; var cntf : TyI);
 var
    i : integer;
    x, y, v, vol : real;

begin
   i :=2;
   vol := 0;
   new_array[1,1] := calc_array[1,1];
   new_array[1,2] := calc_array[1,2];
      while i <= cntf do begin
         new_array[i,1] := calc_array[i,1];
         new_array[i,2] := ((calc_array[i,1] - calc_array[i-1,1]) *
                  calc_array[i-1,2]) + (0.5 * (calc_array[i,1]
                   - calc_array[i-1,1]) * (calc_array[i,2] -
                   calc_array[i-1,2])) + new_array[i-1,2];
         i := i + 1;
      end;
end;

{
**********************************************************************
**** }
procedure adjust_scale   (var ps : real; var work_array : data_array;
                  var s : real; cnt : TyI);
```

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```
var
   i : TyI;
   a,b,j : real;

begin
   i := 1;
   while i <= cnt do begin
      a := work_array[i,1];
      work_array[i,1] := a / ps;
      b := work_array[i,2];
      work_array[i,2] := b * s;
      i := i + 1;
   end;
end;
{
**************************************************************************
**** }

{
**************************************************************************
**** }
Procedure Correct_direc;

var
cnt_corr,
insp,
insp_p : integer;


begin
writeln('IF INSPIRATORY FLOW IS NEGATIVE insp = 1');
writeln('IF INSPIRATORY FLOW IS POSITIVE insp = 2');
writeln('IF INSPIRATORY PRESSURE IS NEGATIVE insp_p = 1');
writeln('IF INSPIRATORY PRESSURE IS POSITIVE insp_p = 2');
```

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```
writeln('PLEASE ENTER CORRECT NUMBER FOR FLOW');
readln(insp);
writeln('PLEASE ENTER CORRECT NUMBER FOR PRESSURE');
readln(insp_p);

if (insp = 1) then
  begin
    if f[3,2] > 0 then
        begin
            cnt_corr := 1;
                while cnt_corr < cnter_f do
                begin
                    f[cnt_corr,2] := f[cnt_corr,2] * (-1);
                    cnt_corr := cnt_corr + 1;
                end;
        end;
  end
 else
    begin
     if f[3,2] > 0 then
        begin
           cnt_corr := 1;
           while cnt_corr < cnter_f do
                begin
                    f[cnt_corr,2] := f[cnt_corr,2] * (-1);
                    cnt_corr := cnt_corr + 1;
                end;
        end;
    end;

if (insp_p = 1) then
  begin
    if p[3,2] > 0 then
        begin
```

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```
            cnt_corr := 1;
                while cnt_corr < cnter_p do
                begin
                    p[cnt_corr,2] := p[cnt_corr,2] * (-1);
                    cnt_corr := cnt_corr + 1;
                end;
        end;
  end
 else
    begin
     if p[3,2] > 0 then
        begin
           cnt_corr := 1;
           while cnt_corr < cnter_p do
                begin
                    p[cnt_corr,2] := p[cnt_corr,2] * (-1);
                    cnt_corr := cnt_corr + 1;
                end;
        end;
    end;
end;
{
**********************************************************************
**** }
procedure Process_Data;
begin
    clear_arrays(f);
    clear_arrays(p);
    clear_arrays(ep);
    Fill_in_c;
    Zero_base(Base_data1,Cnt1);
    Check_Base;
    If Base_Acceptable then
{      Writeln('BASELINE ERROR ACCEPTABLE') else
```

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```
      Writeln('BASELINE ERROR UNACCEPTABLE');}
    Zero_Numbers(f,Cnter_f);
{     writeln('ROTATING THE FLOW DATA');
    writeln;}
    Rotate_Data(f,Cnter_f);
{     Correct_the_flow; }

{     writeln('INTERPOLATING THE FLOW DATA');
    writeln;                          }
    Interpolate_The_Data(f,Cnter_f);
    Zero_Numbers(p,Cnter_p);
{     writeln('ROTATING THE PRESSURE DATA');
    writeln;                          }
    Rotate_Data(p,Cnter_p);
{     writeln('INTERPOLATING THE PRESSURE DATA');}
    Interpolate_The_Data(p,Cnter_p);
    Correct_direc;
{     writeln('FINDING POINTS OF ZERO FLOW');}
    Interpolate_zero_points(cnter_p);
{     writeln('CALCULATING THE ELASTIC PRESSURE');
    Calculate_elastic_pressure;}
    writeln('ENTER PAPER SPEED IN MM/SEC');
    readln(ps);
    writeln('ENTER SCALE OF FLOW TRACE');
    readln(sf);
    sf := sf/0.8;
    adjust_scale(ps,f,sf,cnter_f);
    writeln('ENTER SCALE OF PRESSURE TRACE');
    readln(sp);
    sp := sp/8;
    adjust_scale(ps,p,sp,cnter_p);
    adjust_scale(ps,ep,sp,cnter_ep);
  end;
```

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```
{
**********************************************************************
**** }
begin
    Get_File_Names;

    Process_Data;
{    Calc_volume(f, v, cnter_f);
    writeln;
    writeln('COMPLETING CALCULATIONS');
    writeln;}
    cnter_vol := 1;
    assign(outfile, outfilename);
    rewrite(outfile);
    while cnter_vol <= cnter_f do begin
        writeln(outfile,f[cnter_vol,1]:8:3,' ',f[cnter_vol,2]:8:3,
              ' ', p[cnter_vol,2]:8:3);
        cnter_vol := cnter_vol + 1;
     end;
     close(outfile);
end. { fixit }
```

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Appendix 4.2 Progamme to calculate volume, correct volume drift and do further calculations (Newcalr4)

```
/* PROGRAMME TO CALCULATE VOLUME, CORRECT VOLUME DRIFT
 AND THEN CALCULATE THE  ELASTIC RESISTANCE, AIRWAYS AND
TOTAL RESISTANCE
uses volume as the basis and corrects volume drift using a least squares method
this version does not correct for BTPS
the input file is .d
the output file is .r
 and will also set up fileinfo */


#include <c:\#prog\qc2\include\stdio.h>
#include <c:\#prog\qc2\include\stdlib.h>
#include <c:\#prog\qc2\include\math.h>
#include <string.h>

#define ROWMAX 550
#define COLMAX 7
#define MAXBREATHS 12
#define VERSION "version 1.02"

float data_array[ROWMAX][COLMAX];
float mean_array[MAXBREATHS][2];
char pathname[30] = "fileinfo", pathname1[30], pathname2[30], filename[30];
char *answer, *answer1;
int cnt = 0,i=0, ave, out, check=0;
int breath[ROWMAX][3];
FILE *fp, *fp1, *fp2, *fo;
float a,b;
float *ac, *acc[COLMAX];
int result, info;
```

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```
char *tpt, *newpt;

int Calculate_least_squares(int);
void Calc_correct_factor(int);
void Calc_volume(int);
void Correct_volume(int);
void Define_breaths(int);
void Elastic_pressure(int);
void Airway_resistance(int);

main(void)
{
        int num_means;

        printf("\n\n PROGRAMME TO CORRECT \n FOR VOLUME DRIFT\n
AND CALCULATE ELASTIC PRESSURE AND AIRWAY RESISTANCE
\n\t%s\n", VERSION);
        fo = fopen(pathname, "w");
        if (fo == NULL)
                {
                printf("UNABLE TO OPEN FILEINFO");
                exit(2);
                }


        puts(" PLEASE ENTER THE NAME OF THE DATA FILE: ");
        scanf("%s", filename);
        tpt = strrchr(filename, 'd');
        strcpy(tpt, " ");
/*      fprintf(fo,"%s \n", filename);
        strcpy(tpt, "d");
        fprintf(fo, "%s \n",filename);  */
        strcpy(tpt, "r");
        strcpy(pathname2, filename);
```

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```
        fprintf(fo, "%s \n",filename);
/*      strcpy(tpt, "a");
        fprintf(fo, "%s \n",filename);
        strcpy(tpt, "v");
        fprintf(fo, "%s \n",filename);
        strcpy(tpt, "p");
        fprintf(fo, "%s \n",filename); */
        strcpy(tpt, "d");

 /*     fcloseall;

        fo = fopen(pathname, "r");


        if (fo == NULL){
                printf("UNABLE TO OPEN FILEINFO");
                exit(1);
                }


        info = fscanf(fo, "%s", filename, filename, pathname2, pathname1,
pathname1); */

        ac = &data_array[0][0];

        fp = fopen(filename, "r");  /*open the input file*/

        if (fp == NULL){
                printf("UNABLE TO OPEN %s\n", filename);
                exit(1);
                }
         printf("READING THE DATA FROM: %s\n\n", filename);
         while ((i++ <= ROWMAX) && (!feof(fp))){
                 result = fscanf(fp, "%f %f %f\n",
```

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```
                                &data_array[i][0],
                                &data_array[i][1],
                                &data_array[i][2]);

          }
i = i - 1;
Calc_volume(i);
num_means = Calculate_least_squares(i);

if (num_means == -1)
          exit (2);



Calc_correct_factor(num_means);
Correct_volume(i);
Define_breaths(i);
i = i - 1;
Elastic_pressure(i);
Airway_resistance(i);

fp2 = fopen(pathname2, "w");
if (fp2 == NULL)
          {
          printf("UNABLE TO OPEN %s\n", pathname2);
          exit(1);
          }
 printf("WRITING DATA TO DISC FILE: %s\n", pathname2);
 for(out=0; out < i; ++out)
 {
          fprintf(fp2, "%8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f\n",
                                                  data_array[out][0],
                                                  data_array[out][1],
                                                  data_array[out][2],
                                                  data_array[out][3],
```

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```
                                                    data_array[out][4],
                                                    data_array[out][5],
                                                    data_array[out][6]);

        }

        fcloseall;
}

/*****************************************************************
********/
 /*Function: to integrate flow data to produce volume data*/

 void
 Calc_volume(int v)
 {
 int cntf;
 float volume = 0.0;

 printf("CALCULATING THE VOLUME FROM THE FLOW DATA\n\n");

 for(cntf=1; cntf<v; ++cntf)
        data_array[cntf][3] = 0.0;

 for (cntf=2; cntf<v; ++cntf)
        {
        if (fabs(data_array[cntf][1]) < fabs(data_array[cntf-1][1]))
        volume = (data_array[cntf][0] - data_array[cntf-1][0]) * data_array[cntf][1]
            + 0.5 * ((data_array[cntf][0] - data_array[cntf-1][0]) *
            (data_array[cntf][1] - data_array[cntf-1][1]));
        else
        volume = (data_array[cntf][0] - data_array[cntf-1][0]) * data_array[cntf-1][1]
            + 0.5 * ((data_array[cntf][0] - data_array[cntf-1][0]) *
```

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```
            (data_array[cntf][1] - data_array[cntf-1][1]));

        data_array[cntf][3] = data_array[cntf-1][3] + volume;
        volume = 0.0;
        }
 }
/*****************************************************************
********/

        /* Function to calculate the least squares from the volume */
        /* INPUT:  number of points to consider  */
        /* RETURN: number of breaths detected    */

int Calculate_least_squares(int numrows)
{
 int cntm = 0,m = 0;
 int cntv, ind = 0;
 float vol = 0.0, t = 0.0;

 for(cntv=1; cntv < numrows && ind < MAXBREATHS; ++cntv)
        {
        if (((data_array[cntv][1]) == 0) && (cntv > 2))
           cnt++;

         vol += data_array[cntv][3];
         t += data_array[cntv][0];
         cntm += 1;

         if (cnt == 2)
                {                       /* End of a breath */
                 vol = vol / cntm;
                 t = t / cntm;

                 mean_array[ind][0] = t;
```

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```
                mean_array[ind][1]= vol;
                printf("%f %f\n", mean_array[ind][0], mean_array[ind][1]);
                ind++;

                cnt  = 0;
                cntm = 0;
                t    = 0.0;
                vol  = 0.0;
                }
        }

        if (ind >= MAXBREATHS) {
                puts ("ERROR: Too many breaths in data\n");
                return (-1);
        }
        ind = ind - 1;
        return (ind);
}

/*****************************************************************************
********/
        /* Function to fit curve ax + b */
void
Calc_correct_factor(int numbreaths)
{
        int m, sum, me;
        float a1=0, a2=0, meanx = 0.0, meany = 0.0;

        for(m=0; m <= numbreaths; ++m)
                {
                meanx = meanx + mean_array[m][0];
                meany = meany + mean_array[m][1];
                }
        me = numbreaths + 1;
```

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```
        meanx = meanx / me;
        meany = meany / me;

        for(m=0; m <= numbreaths; ++m)
                {
                a1 = a1 + ((mean_array[m][0] - meanx) * (mean_array[m][1] -
meany));
                a2 = a2 + (mean_array[m][0] - meanx) * (mean_array[m][0] -
meanx);
                }
        a = a1 / a2;
        b = meany - a * (meanx);

        printf("a = %f, \tb = %f\n", a, b);
}
/*************************************************************************
********/
 /* function uses a and b to correct the volume */

 void
 Correct_volume(int count)

{
int vol_cnt = 0;
float temp, t, base;

printf("CORRECTING THE VOLUME FOR DRIFT\n");
while (vol_cnt < count)
  {
  t = data_array[vol_cnt][3] - (a*(data_array[vol_cnt][0]));
  data_array[vol_cnt][3] = t;
  ++vol_cnt;
  }
}
```

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```
/*****************************************************************
******/
void
Define_breaths(int count)
{
int acount=0,bc = 0;

    /* breath[acount][0] will be 0 if flow 0, 1 if inspiration,
                        * 2 if expiration */
    /* breath[acount][1] will be breath number */

breath[acount][1] = 1;
breath[acount][0] = 1;
for(acount = 1; acount < count; ++acount)
        {
        if ((data_array[acount][1] == 0) && (acount > 2))
                {
                switch(breath[acount-1][0])
                        {
                        case 1:
                                breath[acount][0] = 0;
                                breath[acount+1][0] = 2;
                                breath[acount][1] = breath[acount-1][1];
                                breath[acount+1][1] = breath[acount][1];
                                break;
                        case 2:
                                breath[acount][0] = 0;
                                breath[acount+1][0] = 1;
                                breath[acount][1] = breath[acount-1][1] + 1;
                                breath[acount+1][1] = breath[acount][1];
                                break;
                        }
                ++acount;
                }
```

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```
        else
                {
                breath[acount][0] = breath[acount-1][0];
                breath[acount][1] = breath[acount-1][1];
                }
        }
}
/*****************************************************************
*****/
void
Elastic_pressure(int cntep)

{
float press_array[ROWMAX][3];
int count, cepr = 1;

            /*search the data for points of zero flow*/

printf("CALCULATING THE ELASTIC PRESSURE\n");

press_array[0][0] = 0.0;
press_array[0][1] = 0.0;
press_array[0][2] = 0.0;
for(count=1;count<cntep;++count)
        {
        if (breath[count][0] == 0)
                {
                press_array[cepr][0] = data_array[count][0];
                press_array[cepr][1] = data_array[count][2];
                press_array[cepr][2] = data_array[count][3];
                ++cepr;
                }
        }
                /*calculate the elastic pressure as a function of volume and pressure*/
```

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```
cepr = 1;
data_array[0][4] = 0.0;
for(count=1;count<cntep; ++count)
        {
        switch(breath[count][0])
                {
                case 0:
                        data_array[count][4] = data_array[count][2];
                        cepr += 1;
                        break;

                case 1:
                        data_array[count][4] = press_array[cepr-1][1] +
                                        ((press_array[cepr][1] - press_array[cepr-
1][1])
                                        * (data_array[count][3] - press_array[cepr-
1][2])
                                        / (press_array[cepr][2] - press_array[cepr-
1][2]));
                        break;

                case 2:
                        data_array[count][4] = press_array[cepr-1][1] +
                                        ((press_array[cepr][1] - press_array[cepr-
1][1])
                                        * (data_array[count][3] - press_array[cepr-
1][2])
                                        / (press_array[cepr][2] - press_array[cepr-
1][2]));
                        break;
                }

        }
}
```

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```
/*****************************************************************
*****/
void
Airway_resistance(cntar)
{
int count;

printf("CALCULATING THE AIRWAY RESISTANCE\n");

for(count=2;count<cntar;++count)
        {
        if (data_array[count][1] == 0)
                {
                data_array[count][5] = 0;
                data_array[count][6] = 0;
                }
        else
                {
                data_array[count][5] = fabs((data_array[count][2] -
data_array[count][4])
                                        / (data_array[count][1] / 1000));
                data_array[count][6] = fabs(data_array[count][2]
                                        / (data_array[count][1] / 1000));
                }
        }
}
/*****************************************************************
*****/
```

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Appendix 4.3 Programme to interpolate breaths for volume and percent tidal volume (Newbper)

```
/* PROGRAMME TO INTERPOLATE
 * SEVERAL BREATHS FOR VOLUME ON PERCENT TIDAL VOLUME
 * read data from .*r
 * corrects volume for drift
 * converts volume to % tidal volume
 * and interpolates at 5% intervals
 * output to .*p
 * this version includes the additional resistance data */



#include <stdio.h>
#include <string.h>
#include <stdlib.h>
#include <math.h>

#define ROWMAX 550
#define COLMAX 7
#define MAXBREATHS 10
#define VERSION "version 2.02"

float data_array[ROWMAX][COLMAX];
float mean_array[MAXBREATHS][2];
char pathname[30] = "fileinfo", pathname1[30], pathname2[30], filename[30],
file1name[30];
char *answer, *answer1;
int cnt = 0,i=0, ave, out, check=0;
int breath[ROWMAX][3];
FILE *fp, *fp1, *fp2, *fo;
float a,b;
```

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```
float *ac, *acc[COLMAX];
int result, info;

int Calculate_least_squares(int);
void Calc_correct_factor(int);
void Correct_volume(int);
void Define_breaths(int);
void Convert_to_percent(int);
void Interpolate_volumes(int);

main(void)
{
        int num_means;

        printf("\n\n PROGRAMME TO CONVERT TO PERCENT TIDAL
VOLUME\n AND INTERPOLATE SEVERAL BREATHS\n\t %s\n", VERSION);
        fo = fopen(pathname, "r");

        if (fo == NULL){
                printf("UNABLE TO OPEN FILEINFO");
                exit(1);
                }
   /*   info = fscanf(fo, "%s %s %s %s %s %s", filename, filename, filename,
pathname1, file1name, pathname2); */

        info = fscanf(fo, "%s", filename);
        strcpy(pathname2, filename);
        answer1 = strrchr(pathname2,'r');
        strcpy(answer1, "p");
        ac = &data_array[0][0];

        fp = fopen(filename, "r");  /*open the input file*/

        if (fp == NULL){
```

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```
                printf("UNABLE TO OPEN %s\n", filename);
                exit(1);
                }
        printf("READING THE DATA FROM: %s\n", filename);
        while ((i++ <= ROWMAX) && (!feof(fp))){
                 result = fscanf(fp, "%f %f %f %f %f %f %f\n",
                                        &data_array[i][0],
                                        &data_array[i][1],
                                        &data_array[i][2],
                                        &data_array[i][3],
                                        &data_array[i][4],
                                        &data_array[i][5],
                                        &data_array[i][6]);

                 }
        i = i - 1;
/*      num_means = Calculate_least_squares(i);

        if (num_means == -1)
                exit (2);

        Calc_correct_factor(num_means);
        Correct_volume(i);*/
        Define_breaths(i);
        Convert_to_percent(i);
        i = i - 1;
        Interpolate_volumes(i);

        fp2 = fopen(pathname2, "w");
        if (fp2 == NULL)
                {
                printf("UNABLE TO OPEN %s\n", pathname2);
                exit(1);
                }printf("WRITING DATA TO DISC FILE: %s\n", pathname2);
```

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```
        for(out=0; out < i; ++out)
        {
                fprintf(fp2, "%8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %d %d\n",
                                                        data_array[out][0],
                                                        data_array[out][1],
                                                        data_array[out][2],
                                                        data_array[out][3],
                                                        data_array[out][4],
                                                        data_array[out][5],
                                                        data_array[out][6],
                                                        breath[out][0],
                                                        breath[out][1]);

        }

        fcloseall;
}

/*****************************************************************
********/
        /* Function to calculate the least squares from the volume */
        /* INPUT:  number of points to consider  */
        /* RETURN: number of breaths detected    */

int Calculate_least_squares(int numrows)
{
 int cntm = 0,m = 0;
 int cntv, ind = 0;
 float vol = 0.0, t = 0.0;

 for(cntv=1; cntv < numrows && ind < MAXBREATHS; ++cntv)
        {
        if (((data_array[cntv][1]) == 0) && (cntv > 2))
           cnt++;
```

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```
        vol += data_array[cntv][3];
        t += data_array[cntv][0];
        cntm += 1;

        if (cnt == 2)
                {                       /* End of a breath */
                vol = vol / cntm;
                t = t / cntm;

                mean_array[ind][0] = t;
                mean_array[ind][1]= vol;
                printf("%f %f\n", mean_array[ind][0], mean_array[ind][1]);
                ind++;

                cnt  = 0;
                cntm = 0;
                t    = 0.0;
                vol  = 0.0;
                }
        }

        if (ind >= MAXBREATHS) {
                puts ("ERROR: Too many breaths in data\n");
                return (-1);
        }
        ind = ind - 1;
        return (ind);
}

/*****************************************************************
********/
        /* Function to fit curve ax + b */
void
```

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```
Calc_correct_factor(int numbreaths)
{
        int m, sum, me;
        float a1=0, a2=0, meanx=0.0, meany=0.0;

        for(m=0; m <= numbreaths; ++m)
                {
                meanx = meanx + mean_array[m][0];
                meany = meany + mean_array[m][1];
                }
        me = numbreaths + 1;
        meanx = meanx / me;
        meany = meany / me;

        for(m=0; m <= numbreaths; ++m)
                {
                a1 = a1 + ((mean_array[m][0] - meanx) * (mean_array[m][1] -
meany));
                a2 = a2 + (mean_array[m][0] - meanx) * (mean_array[m][0] -
meanx);
                }
        a = a1 / a2;
        b = meany - a * (meanx);

        printf("a = %f, \tb = %f\n", a, b);
}
/*****************************************************************************
********/
 /* function uses a and b to correct the volume */

 void
 Correct_volume(int count)

{
```

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```
int vol_cnt = 0;
float temp, t, base;

printf("CORRECTING THE VOLUME FOR DRIFT\n");
while (vol_cnt < count)
  {
  t = data_array[vol_cnt][3] - (a*(data_array[vol_cnt][0]));
  data_array[vol_cnt][3] = t;
  ++vol_cnt;
  }
}
/*****************************************************************
******/
void
Define_breaths(int count)
{
int acount=0,bc = 0;

    /* breath[acount][0] will be 0 if flow 0, 1 if inspiration,
                        * 2 if expiration */
    /* breath[acount][1] will be breath number */

printf("DEFINING BREATHS\n");
breath[acount][1] = 1;
breath[acount][0] = 1;
for(acount = 1; acount < count; ++acount)
        {
        if ((data_array[acount][1] == 0) && (acount > 2))
                {
                switch(breath[acount-1][0])
                        {
                        case 1:
                                breath[acount][0] = 0;
                                breath[acount+1][0] = 2;
```

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```
                                breath[acount][1] = breath[acount-1][1];
                                breath[acount+1][1] = breath[acount][1];
                                break;
                        case 2:
                                breath[acount][0] = 0;
                                breath[acount+1][0] = 1;
                                breath[acount][1] = breath[acount-1][1] + 1;
                                breath[acount+1][1] = breath[acount][1];
                                break;
                        }
                 ++acount;
                 }
        else
                {
                breath[acount][0] = breath[acount-1][0];
                breath[acount][1] = breath[acount-1][1];
                }
        }
}
//*****************************************************************************
*****/
void
Convert_to_percent(int cntp)
{
 float least = 0.0, min = 0.0, total = 0.0;
 float temp;
 int pcount = 0;

printf("CONVERTING VOLUME TO PERCENT TIDAL VOLUME\n");
while (breath[pcount][1] == 1)
        {
        if (data_array[pcount][3] < least) least = data_array[pcount][3];
        pcount = pcount + 1;
        }
```

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```
 least = fabs(least);
 for(pcount = 0; pcount < cntp; ++pcount)
          {
           temp = ((data_array[pcount][3]) / least) * 100;
           data_array[pcount][3] = temp;
          }
}
/*********************************************************************
*****/
void
Interpolate_volumes(int interc)
{
int count = 1, new = 0, newcount, c, end;
int incr = 5, sign = (1);
float new_array[ROWMAX][COLMAX];
int new_breath[ROWMAX][2];
float newincr;

 while(new <ROWMAX)
          {
          for(c=0;c<COLMAX;++c)
                    {
                    new_array[new][c] = 0.0;
                    new_breath[new][0] = 0;
                    new_breath[new][1] = 0;
                    }
           ++new;
           }
 new = 0;
/* printf("PLEASE ENTER THE INCREMENT INTERVAL:  ");

 scanf("%d", &incr);*/
 printf("INCREMENT IS: %d\n",incr);
 printf("INTERPOLATING VOLUME VALUES\n");
```

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```
new_array[new][0] = data_array[count][0];  /*initializing the array*/
new_array[new][1] = data_array[count][1];
new_array[new][2] = data_array[count][2];
new_array[new][3] = data_array[count][3];
new_array[new][4] = data_array[count][4];
new_array[new][5] = data_array[count][5];
new_array[new][6] = data_array[count][6];
new_breath[new][0] = breath[count][0];
new_breath[new][1] = breath[count][1];

for(count=0; count < interc; ++count)
        {
        while ((data_array[count+1][1] == 0) && (count < 2)) ++count;

        switch(breath[count+1][0])
        {
        case  0:
                if (fabs(data_array[count+1][3] - new_array[new][3]) <= incr)
                        {
                        new_array[new+1][0] = data_array[count+1][0];
                        new_array[new+1][1] = data_array[count+1][1];
                        new_array[new+1][2] = data_array[count+1][2];
                        new_array[new+1][3] = data_array[count+1][3];
                        new_array[new+1][4] = data_array[count+1][4];
                        new_array[new+1][5] = data_array[count+1][5];
                        new_array[new+1][6] = data_array[count+1][6];
                        new_breath[new+1][0] = breath[count+1][0];
                        new_breath[new+1][1] = breath[count][1];
                        ++count;
                        ++new;

                        new_array[new+1][3] = new_array[new-1][3];
                        while (fabs(data_array[count+1][3] - new_array[new][3]) <
```

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```
                    fabs(new_array[new+1][3] - new_array[new][3])) ++count;

                    new_array[new+1][0] = new_array[new][0] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][0] -
new_array[new][0])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][1] = new_array[new][1] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][1] -
new_array[new][1])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][2] = new_array[new][2] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][2] -
new_array[new][2])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][4] = new_array[new][4] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][4] -
new_array[new][4])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][5] = new_array[new][5] +
                                        ((new_array[new+1][3] -
new_array[new][3])
```

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```
                                        * (data_array[count+1][5] -
new_array[new][5])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][6] = new_array[new][6] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][6] -
new_array[new][6])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_breath[new+1][0] = breath[count+1][0];
                    new_breath[new+1][1] = breath[count+1][1];
                    ++new;
                    break;
                    }

          if (fabs(data_array[count+1][3] - new_array[new][3]) > incr)
          /* interpolate until the first if condition is met*/

                    {
                    if (new_breath[new][0] == 1) sign = -1;
                              else sign = 1;

                    while(fabs(data_array[count+1][3] - new_array[new][3]) >
incr)
                              {
                              new_array[new+1][3] = new_array[new][3] + (incr *
sign);

                              new_array[new+1][0] = new_array[new][0] +
                                        ((new_array[new+1][3] -
new_array[new][3])
```

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```
                                        * (data_array[count+1][0] -
new_array[new][0])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][1] = new_array[new][1] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][1] -
new_array[new][1])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][2] = new_array[new][2] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][2] -
new_array[new][2])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][4] = new_array[new][4] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][4] -
new_array[new][4])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][5] = new_array[new][5] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][5] -
new_array[new][5])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][6] = new_array[new][6] +
```

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```
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][6] -
new_array[new][6])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_breath[new+1][0] = new_breath[new][0];
                        new_breath[new+1][1] = new_breath[new][1];
                        ++new;
                        }
                /*now do what has been done in the first condition*/
                        new_array[new+1][0] = data_array[count+1][0];
                        new_array[new+1][1] = data_array[count+1][1];
                        new_array[new+1][2] = data_array[count+1][2];
                        new_array[new+1][3] = data_array[count+1][3];
                        new_array[new+1][4] = data_array[count+1][4];
                        new_array[new+1][5] = data_array[count+1][5];
                        new_array[new+1][6] = data_array[count+1][6];
                        new_breath[new+1][0] = breath[count+1][0];
                        new_breath[new+1][1] = breath[count][1];
                        ++count;
                        ++new;

                        new_array[new+1][3] = new_array[new-1][3];
                        while (fabs(data_array[count+1][3] - new_array[new][3]) <
                        fabs(new_array[new+1][3] - new_array[new][3])) ++count;

                        new_array[new+1][0] = new_array[new][0] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][0] -
new_array[new][0])
                                        / (data_array[count+1][3] -
new_array[new][3]));
```

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```
                    new_array[new+1][1] = new_array[new][1] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][1] -
new_array[new][1])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][2] = new_array[new][2] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][2] -
new_array[new][2])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][4] = new_array[new][4] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][4] -
new_array[new][4])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][5] = new_array[new][5] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][5] -
new_array[new][5])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][6] = new_array[new][6] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][6] -
new_array[new][6])
```

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```
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_breath[new+1][0] = breath[count+1][0];
                        new_breath[new+1][1] = breath[count][1];
                        ++new;
                        }
                  break;


        case 1:
                new_array[new+1][3] = (new_array[new][3] - incr);
                if (data_array[count+1][3] == new_array[new+1][3])
                        {
                        new_array[new+1][0] = data_array[count +1][0];
                        new_array[new+1][3] = data_array[count +1][3];
                        new_array[new+1][1] = data_array[count +1][1];
                        new_array[new+1][2] = data_array[count +1][2];
                        new_array[new+1][4] = data_array[count +1][4];
                        new_array[new+1][5] = data_array[count +1][5];
                        new_array[new+1][6] = data_array[count +1][6];
                        new_breath[new+1][0] = breath[count+1][0];
                        new_breath[new+1][1] = breath[count+1][1];
                        ++new;
                        break;
                        }
                if (fabs(data_array[count+1][3] - new_array[new][3]) > incr)
                        {
                        new_array[new+1][0] = new_array[new][0] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][0] -
new_array[new][0])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][1] = new_array[new][1] +
```

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```
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][1] -
new_array[new][1])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][2] = new_array[new][2] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][2] -
new_array[new][2])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][4] = new_array[new][4] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][4] -
new_array[new][4])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][5] = new_array[new][5] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][5] -
new_array[new][5])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][6] = new_array[new][6] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][6] -
new_array[new][6])
                                        / (data_array[count+1][3] -
new_array[new][3]));
```

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```
                new_breath[new+1][0] = breath[count+1][0];
                new_breath[new+1][1] = breath[count+1][1];
                ++new;
                break;
                }
        if (fabs(data_array[count+1][3] - new_array[new][3]) < incr)
                {
                while((data_array[count+1][3] > new_array[new+1][3])
                && (data_array[count+1][1] != 0.0))
                        {
                        ++count;
                        }
                count = count - 1;
                break;
                }
        break;
case 2:
        new_array[new+1][3] = new_array[new][3] + incr;
        if (data_array[count+1][3] == new_array[new+1][3])
                {
                new_array[new+1][0] = data_array[count +1][0];
                new_array[new+1][3] = data_array[count +1][3];
                new_array[new+1][1] = data_array[count +1][1];
                new_array[new+1][2] = data_array[count +1][2];
                new_array[new+1][4] = data_array[count +1][4];
                new_array[new+1][5] = data_array[count +1][5];
                new_array[new+1][6] = data_array[count +1][6];
                new_breath[new+1][0] = breath[count+1][0];
                new_breath[new+1][1] = breath[count+1][1];
                ++new;
                break;
                }
        if (fabs(data_array[count+1][3] - new_array[new][3]) > incr)
                {
```

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```
                    new_array[new+1][0] = new_array[new][0] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][0] -
new_array[new][0])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][1] = new_array[new][1] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][1] -
new_array[new][1])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][2] = new_array[new][2] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][2] -
new_array[new][2])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][4] = new_array[new][4] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][4] -
new_array[new][4])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                    new_array[new+1][5] = new_array[new][5] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][5] -
new_array[new][5])
```

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```
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_array[new+1][6] = new_array[new][6] +
                                        ((new_array[new+1][3] -
new_array[new][3])
                                        * (data_array[count+1][6] -
new_array[new][6])
                                        / (data_array[count+1][3] -
new_array[new][3]));
                        new_breath[new+1][0] = breath[count+1][0];
                        new_breath[new+1][1] = breath[count+1][1];
                        ++new;
                        break;
                        }
                if (fabs(data_array[count+1][3] - new_array[new][3]) > incr)
                        {
                        while((data_array[count+1][3] < new_array[new+1][3])
                        && (data_array[count+1][1] != 0.0)) ++count;
                        count = count - 1;
                        break;
                        }
                }
        }
 for(newcount=0; newcount < new; ++newcount)
        {
        data_array[newcount][0] = new_array[newcount][0];
        data_array[newcount][1] = new_array[newcount][1];
        data_array[newcount][2] = new_array[newcount][2];
        data_array[newcount][3] = new_array[newcount][3];
        data_array[newcount][4] = new_array[newcount][4];
        data_array[newcount][5] = new_array[newcount][5];
        data_array[newcount][6] = new_array[newcount][6];
        breath[newcount][0] = new_breath[newcount][0];
        breath[newcount][1] = new_breath[newcount][1];
```

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```
        }
end = newcount;
i = end;
for(newcount=new; newcount<interc; ++newcount)
        {
        data_array[newcount][0] = 0.0;
        data_array[newcount][1] = 0.0;
        data_array[newcount][2] = 0.0;
        data_array[newcount][3] = 0.0;
        data_array[newcount][4] = 0.0;
        data_array[newcount][5] = 0.0;
        data_array[newcount][6] = 0.0;
        }

}
```

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Appendix 4.4 Programme to calculate mean tidal volume and peak tidal volume, flow and pressure (newavol3)

```
/* PROGRAMME TO CALCULATE MEAN TIDAL VOLUME AND PEAK
FLOW AND PRESSURES
 * uses volume and pressure
 * reads from .r and writes to .vol */



#include <c:\#prog\qc2\include\stdio.h>
#include <c:\#prog\qc2\include\stdlib.h>
#include <c:\#prog\qc2\include\math.h>
#include <c:\#prog\qc2\include\string.h>

#define ROWMAX 700
#define COLMAX 7
#define MAXBREATHS 15
#define VERSION "version 1.1"

float data_array[ROWMAX][COLMAX];
char pathname[30] = "fileinfo", filename[30], filename1[30], filename2[30],
filename3[30];
char *answer, *answer1;
int  i=0, ave, out, check=0, cnt=0;
int breath[ROWMAX][3];
FILE *fp, *outfile, *fp2, *fo;
float *ac;
int result, info;
char *tpt, *newpt;

void Define_breaths(int);
void Calculate_vol(int);
```

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```
void Press_flow_peak(int);

main(void)
{
        int num_means;

        printf("\n\n PROGRAMME TO CALCULATE AVERAGE TIDAL
VOLUME\n");
        printf("\t\t%s\n", VERSION);

        fo = fopen(pathname, "r");

        if(fo ==NULL)
                {
                printf("UNABLE TO OPEN FILEINFO");
                exit(1);
                }

        info = fscanf(fo, "%s", filename1);
        fclose(fo);

        ac = &data_array[0][0];

        fp = fopen(filename1, "r");  /*open the input file*/

        if (fp == NULL){
                printf("UNABLE TO OPEN %s\n", filename1);
                exit(1);
                }
         printf("READING THE DATA FROM: %s\n", filename1);
         while ((i++ <= ROWMAX) && (!feof(fp)))
                {
                 result = fscanf(fp, "%f %f %f %f %f %f %f \n",
                                        &data_array[i][0],
```

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```
                                &data_array[i][1],
                                &data_array[i][2],
                                &data_array[i][3],
                                &data_array[i][4],
                                &data_array[i][5],
                                &data_array[i][6]);
            }

i = i - 1;
strcpy(filename2, filename1);
tpt = strchr(filename2,'.');
newpt = strrchr(filename2, 'r');
cnt = fabs(tpt - newpt);
cnt = cnt-1;
if (cnt == 1)
            {
            *tpt = *(newpt-1);
            strcpy(tpt+1, ".vol");
            }
if (cnt == 2)
            {
            *tpt = *(newpt-2);
            *(tpt+1) = *(newpt-1);
            strcpy(tpt+2, ".vol");
            }
if (cnt == 3)
            {
            *tpt = *(newpt-3);
            *(tpt+1) = *(newpt-2);
            *(tpt + 2) = *(newpt-3);
            strcpy(tpt+3, ".vol");
            }
strcpy(filename3, filename2);
tpt = strchr(filename3, '.');
```

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```
        strcpy(tpt + 1, "ppf");

        Define_breaths(i);
        Calculate_vol(i);
        Press_flow_peak(i);
        fcloseall;
}
/*****************************************************************
******/
void
Define_breaths(int count)
{
int acount=0,bc = 0;

    /* breath[acount][0] will be 0 if flow 0, 1 if inspiration,
                        * 2 if expiration */
    /* breath[acount][1] will be breath number */

breath[acount][1] = 1;
breath[acount][0] = 1;
for(acount = 1; acount < count; ++acount)
        {
        if ((data_array[acount][1] == 0) && (acount > 2))
                {
                switch(breath[acount-1][0])
                        {
                        case 1:
                                breath[acount][0] = 0;
                                breath[acount+1][0] = 2;
                                breath[acount][1] = breath[acount-1][1];
                                breath[acount+1][1] = breath[acount][1];
                                break;
                        case 2:
                                breath[acount][0] = 0;
```

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```
                                breath[acount+1][0] = 1;
                                breath[acount][1] = breath[acount-1][1] + 1;
                                breath[acount+1][1] = breath[acount][1];
                                break;
                        }
                ++acount;
                }
        else
                {
                breath[acount][0] = breath[acount-1][0];
                breath[acount][1] = breath[acount-1][1];
                }
        }
}

/*****************************************************************************
*****/
void
Calculate_vol(int cnta)
{
float vol[MAXBREATHS];
int acnt = 1, cnt = 0, mark;
int max, b = 1, breaths;
float min=0.0, great, least, v = 0.0;
float ave_vol = 0.0, mean_vol = 0.0, var, vare = 0.0, varem, std_vol,  sem_vol;

printf("CALCULATING TIDAL VOLUME AND WRITING TO %s\n", filename2);

outfile =  fopen(filename2, "a");  /*open the output file*/

if (outfile == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename2);
        exit(1);
```

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```
        }

/* for each breath identify tidal volume and average */
for (acnt = 1; acnt < cnta; ++ acnt)
        {
        switch (breath[acnt][0])
                {
                case 1 :
                        {
                        break;
                        }
                case 2 :
                        {
                        break;
                        }
                case 0 :
                /* when value calculated place into array */
                        {
                        if (breath[acnt-1][0] == 2)
                                {
                                v = data_array[acnt][3];
                                break;
                                }
                        else
                                {
                                vol[cnt] = fabs(data_array[acnt][3] - v);
                                v = 0.0;
                                ++cnt;
                                break;
                                }
                        }
                }
        }
b = cnt;
```

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```
for (ave = 0; ave < b; ++ ave)
        {
        ave_vol = ave_vol + vol[ave];
        }
mean_vol = ave_vol / b;
printf("VOLUME \t STD \t SEM \t BREATHS \n");
/* fprintf(outfile, "VOLUME \t STD \t SEM \t BREATHS \n"); */
fprintf(outfile, "%8.3f ", mean_vol);
printf("%8.3f ", mean_vol);

if (b <= 1)
        {
        fprintf(outfile, "ONLY ONE BREATH     ");
        printf("ONLY ONE BREATH     ");
        }
else
        {
        for (ave = 0; ave < b; ++ ave)
                {
                var = mean_vol - vol[ave];
                varem = var * var;
                vare = vare + varem;
                }
        vare = vare / b;
        std_vol = sqrt(vare);
        sem_vol = std_vol / (sqrt(b - 1));
        printf("%8.3f %8.3f %d \n", std_vol, sem_vol, b);
        fprintf(outfile, "%8.3f %8.3f %d ", std_vol, sem_vol, b);
        }
fclose(outfile);
}
/*****************************************************************
*****/
void
```

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```
Press_flow_peak(int pt)

{
float mean[4];
float var[4], varem[4], vare[4];
float maxp[4][MAXBREATHS];
float me = 0.0, v = 0.0;
int cntpt, ave = 1, maxe = 0, maxi = 0, max, cnt;

outfile =  fopen(filename2, "a");  /*open the output file which is now the same
                                        as the volume file */

if (outfile == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename2);
        exit(1);
        }


printf("CALCULATING AVERAGE PEAK PRESSURES AND FLOWS\n");
printf("AND WRITING TO %s \n", filename2);
printf("\t INSPF\t EXPF\t INSPP\t EXPP \n");
/* fprintf(outfile, "  INSPF   STD   SEM   EXPF   STD   SEM   INSPP   STD
SEM   EXPP   STD   SEM \n"); */

printf("MEAN: \t");

for(max = 0;max <=3; ++max)       /*setting array to zero*/
        {
        for (ave =0; ave< MAXBREATHS; ++ave)
                {
                maxp[max][ave] = 0.0;
                }
        }
```

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```
max = 0;

for(cntpt=1; cntpt < pt; ++cntpt)    /*selecting the points of max flow and press */
        {
        switch (breath[cntpt][0])
                {
                case 1 :   /* selecting inspiratory points
                            0 = insp flow
                            1 = exp flow
                            2 = insp press
                            3 = exp press */
                        {
                        if (data_array[cntpt][1] < maxp[0][maxi])
                                maxp[0][maxi] = data_array[cntpt][1];
                        if (data_array[cntpt][2] < maxp[2][maxi])
                                maxp[2][maxi] = data_array[cntpt][2];
                        break;
                        }
                case 2 :   /* selecting expiratory points */
                        {
                        if (data_array[cntpt][1] > maxp[1][maxe])
                                maxp[1][maxe] = data_array[cntpt][1];
                        if (data_array[cntpt][2] > maxp[3][maxe])
                                maxp[3][maxe] = data_array[cntpt][2];
                        break;
                        }

                case 0 :
                        {
                        if (breath[cntpt-1][0] == 2)
                             {
                                ++maxe;
                                break;
                                }
```

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```
                    else
                        {
                        ++maxi;
                        break;
                        }
                    }
                }
            }
if (maxi >= maxe) max = maxe;
if (maxe > maxi) max = maxi;
max = max - 1;

for (cnt=0; cnt<=4;++cnt)       /* set array of means to zero */
            {
            mean[cnt] = 0.0;
            var[cnt] = 0.0;
            vare[cnt] = 0.0;
            }
for (cnt = 0; cnt <= 3; ++cnt)
            {
             for (ave = 0; ave <= max; ++ ave)
                    {
                     me = me + maxp[cnt][ave];

                    }
             mean[cnt] = me;
             me = 0.0;
            }
for (cnt = 0; cnt <= 3; ++cnt)
            {
            mean[cnt] = mean[cnt] / (max + 1);
            printf("%8.3f", mean[cnt]);
            }
```

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```
printf("\n STD: \t");

if (max == 0)
        {
        fprintf(outfile, "ONLY ONE BREATH     ");
        printf("ONLY ONE BREATH     ");
        }
else
        {
        for (cnt = 0; cnt <= 3; ++cnt)
                {
                for (ave = 0; ave <= max; ++ ave)
                        {
                        var[cnt] = mean[cnt] - maxp[cnt][ave];
                        var[cnt] = var[cnt] * var[cnt];
                        v = v + var[cnt];
                        }
                vare[cnt] = v;
                v = 0.0;
                }
        for (cnt = 0; cnt <= 3; ++cnt)
                {
                var[cnt] = vare[cnt] / (max + 1);
                var[cnt] = sqrt(var[cnt]);
                printf("%8.3f ", var[cnt]);
                }
        printf("\n SEM: \t");
        for (cnt = 0; cnt <= 3; ++cnt)
                {
                vare[cnt] = var[cnt] / (sqrt(max));
                printf("%8.3f ", vare[cnt]);
                }
        for (cnt = 0; cnt <= 3; ++cnt)
                {
```

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```
                fprintf(outfile, "%8.3f %8.3f %8.3f ", mean[cnt], var[cnt], vare[cnt]);
                }
        }
fclose(outfile);
}
/*************************************************************************
*****/
```

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Appendix 4.5 Programme to calculate the average for several breaths (Newasum1)

```
/* PROGRAMME TO CALCULATE THE AVERAGE
 * OF SEVERAL BREATHS
 * reads the data from .*p and
 * outputs to *.sum
 * and *.pav
 * this version includes resistance (not corrected for compliance */



#include <stdio.h>
#include <stdlib.h>
#include <math.h>
#include <string.h>

#define ROWMAX 700
#define COLMAX 7
#define MAXBREATHS 10
#define VERSION "version 1.02"

float data_array[ROWMAX][COLMAX];
float mean_array[MAXBREATHS][2];
char pathname[30] = "fileinfo", filename[30], filename1[30], filename2[30];
char *answer, *answer1;
int cnt = 0, i=0, ave, out, check=0;
int breath[ROWMAX][3];
FILE *fp, *outfile, *outfile1, *fp2, *fo;
float a,b;
float *ac, *acc[COLMAX];
int result, info;
char *tpt, *newpt;
```

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```
void Average_values(int);

main(void)
{
        int num_means;

        printf("\n\n PROGRAMME TO AVERAGE DATA FROM SEVERAL
BREATHS\n AND STORE DATA AT 25 PERCENT INTERVALS\n");
        printf("\t\t %s\n", VERSION);

        fo = fopen(pathname, "r");

        if(fo ==NULL)
                {
                printf("UNABLE TO OPEN FILEINFO");
                exit(1);
                }
 /*   info = fscanf(fo, "%s %s %s %s %s %s", filename, filename, filename1,
filename, filename, filename); */

        info = fscanf(fo, "%s", filename);
        tpt = strrchr(filename, 'r');
        strcpy(tpt, "p");
        strcpy(filename1, filename);

        tpt = strchr(filename1, '.');
        newpt = strrchr(filename1, 'p');
        cnt = fabs(tpt-newpt);
        cnt = cnt - 1;
        if (cnt == 1)
                {
                *tpt = *(newpt-1);
                tpt = tpt + 1;
                strcpy(tpt, ".pav");
```

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```
            }
        if (cnt == 2)
            {
            *tpt = *(newpt-2);
            *(tpt+1) = *(newpt-1);
            tpt = tpt + 2;
            strcpy(tpt, ".pav");
            }
        if (cnt == 3)
            {
            *tpt = *(newpt-2);
            *(tpt+1) = *(newpt-1);
            *(tpt+2) = *(newpt-2);
            tpt = tpt + 3;
            strcpy(tpt, ".pav");
            }
         strcpy(filename2, filename1);
         tpt = strchr(filename2,'.');
         strcpy(tpt, ".sum");

        cnt = 0;


/*    puts("PLEASE ENTER THE NAME OF THE DATA FILE: ");
        scanf("%s", filename);

        strcpy(filename1, filename);
        tpt = strchr(filename1, '.');
        *tpt = *(tpt+1);
        strcpy(tpt+1, ".pav");
        strcpy(filename2, filename1);
        tpt = strchr(filename2, '.');
        strcpy(tpt, ".sum");                    */
```

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```
 /*     puts("PLEASE ENTER THE NAME OF THE OUTPUT FILE: ");
        scanf("%s", filename1);
        puts("PLEASE ENTER THE NAME OF THE SUMMARY FILE: ");
        scanf("%s", filename2);*/


        ac = &data_array[0][0];

        fp = fopen(filename, "r");  /*open the input file*/

        if (fp == NULL){
                printf("UNABLE TO OPEN %s\n", filename);
                exit(1);
                }
         printf("READING THE DATA FROM: %s\n", filename);
         while ((i++ <= ROWMAX) && (!feof(fp)))
                {
                 result = fscanf(fp, "%f %f %f %f %f %f %d %d\n",
                                        &data_array[i][0],
                                        &data_array[i][1],
                                        &data_array[i][2],
                                        &data_array[i][3],
                                        &data_array[i][4],
                                        &data_array[i][5],
                                        &data_array[i][6],
                                        &breath[i][0],
                                        &breath[i][1]);
        /*          printf("%d %d %f %f\n", i, breath[i][1], data_array[i][0],
data_array[i][1]);*/
                 }
         Average_values(i);

         fcloseall;
}
```

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```
/*****************************************************************
*****/
void
Average_values(int cnta)
{
float vol;
int ind, br = 0, nat, tan;
float max=0.0, min=0.0, great, least;
float var, vare, sum, varem;
float var_array[10], mean_array[10], ave_array[10][10], varem_array[10];

printf("AVERAGING VALUES AND WRITING TO  %s \n \t \t \t %s\n",
filename1, filename2);

outfile =  fopen(filename1, "w");  /*open the output file*/
outfile1 =  fopen(filename2, "w");  /*open the output file for summary data*/

if (outfile == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename1);
        exit(1);
        }
if (outfile1 == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename2);
        exit(1);
        }

ave = 1;
while (breath[ave][1] == 1)   /*start the averaging process*/
        {
        vol = data_array[ave][3];
        ave_array[1][0] = data_array[ave][1];
```

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```
ave_array[2][0] = data_array[ave][2];
ave_array[3][0] = data_array[ave][3];
ave_array[4][0] = data_array[ave][4];
ave_array[5][0] = data_array[ave][5];
ave_array[6][0] = data_array[ave][6];
br = 1;
for (ind = ave + 1; ind <cnta ; ++ind)

        {
        if ((data_array[ind][3] == vol) &&
        (breath[ind][1] > breath[ave][1]) &&
        (breath[ind][0] == breath[ave][0]))
                {
                ave_array[1][br] = data_array[ind][1];
                ave_array[2][br] = data_array[ind][2];
                ave_array[3][br] = data_array[ind][3];
                ave_array[4][br] = data_array[ind][4];
                ave_array[5][br] = data_array[ind][5];
                ave_array[6][br] = data_array[ind][6];
                ++br;
                }
        }
if (br > 0)
        {
        for(nat = 1; nat <= 6; ++nat)
             {
             sum = 0;
             for(tan = 0; tan < br; ++tan) sum = ave_array[nat][tan] + sum;
             mean_array[nat] = sum / br;
             }

        for(nat = 1; nat <= 6; ++nat)
             {
             var = 0;
```

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```
                for(tan = 0; tan < br; ++tan)
                        {
                        vare = mean_array[nat] - ave_array[nat][tan];
                        vare = vare * vare;
                        var = var + vare;
                        }
                var = var / br;
                var_array[nat] = sqrt(var);
                varem = var_array[nat] / sqrt(br);
                varem_array[nat] = varem;
                    }
            }
            fprintf(outfile, "%8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f
%8.3f %8.3f %d\n",
                                mean_array[1], varem_array[1],
                                mean_array[2], varem_array[2],
                                data_array[ave][3],
                                mean_array[4],
                                mean_array[5], varem_array[5],
                                mean_array[6], varem_array[6],
                                br);
            if (fmod(data_array[ave][3], 25) == 0)
            fprintf(outfile1, "%8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f
%8.3f %8.3f %d\n",
                                mean_array[1], varem_array[1],
                                mean_array[2], varem_array[2],
                                data_array[ave][3],
                                mean_array[4],
                                mean_array[5], varem_array[5],
                                mean_array[6], varem_array[6],
                                br);
            ++ave;
            }
fclose (outfile);
```

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```
fclose (outfile1);
}
/*****************************************************************************
*****/
```

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Appendix 4.6 Programme to calculate the work of breathing (Avework4)

```
/* PROGRAMME TO CALCULATE THE WORK OF BREATHING
 * uses volume and pressure to calculate the resistive
 * work of breathing, and pressure and time to calculate
 * the pressure time integral
 * this version separates inspiratory and expiratory ptint
 * Reads .r and outputs to vol (appending the data)
 * Corrected for error in the integration programme*/



#include <c:\#prog\qc2\include\stdio.h>
#include <c:\#prog\qc2\include\stdlib.h>
#include <c:\#prog\qc2\include\math.h>
#include <c:\#prog\qc2\include\string.h>

#define ROWMAX 700
#define COLMAX 7
#define MAXBREATHS 15
#define VERSION "version 1.04"

float data_array[ROWMAX][COLMAX];
float mean_array[MAXBREATHS][2];
char pathname[30] = "fileinfo", filename[30], filename1[30], filename2[30];
char *answer, *answer1;
int cnt = 0, i=0, ave, out, check=0;
int breath[ROWMAX][2];
FILE *fp, *outfile, *fp2, *fo;
float *ac, *acc[COLMAX];
int result, info;
char *tpt, *newpt;
```

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```
void Mark_breaths(int);
void Calculate_work(int);
void Press_time_integral(int);

main(void)
{
        int num_means;

        printf("\n\n PROGRAMME TO CALCULATE WORK OF BREATHING
FROM THE r FILE\n");
        printf("\t\t%s\n", VERSION);

    /*  puts("PLEASE ENTER THE NAME OF THE DATA FILE: ");
        scanf("%s", filename);                    */

        fo = fopen(pathname, "r");

        if(fo ==NULL)
                {
                printf("UNABLE TO OPEN FILEINFO");
                exit(1);
                }
  /*    info = fscanf(fo, "%s %s %s %s %s %s", filename, filename, filename1,
filename, filename, filename); */

        info = fscanf(fo, "%s",  filename1);
        fp = fopen(filename1, "r");  /*open the input file*/

        if (fp == NULL){
                printf("UNABLE TO OPEN %s\n", filename1);
                exit(1);
                }
         printf("READING THE DATA FROM: %s\n", filename1);
```

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```
 while ((i++ <= ROWMAX) && (!feof(fp)))
        {
         result = fscanf(fp, "%f %f %f %f %f %f %f\n",
                              &data_array[i][0],
                              &data_array[i][1],
                              &data_array[i][2],
                              &data_array[i][3],
                              &data_array[i][4],
                              &data_array[i][5],
                              &data_array[i][6]);
         }

tpt = strchr(filename1, '.');
newpt = strrchr(filename1, 'r');
cnt = fabs(tpt-newpt);
cnt = cnt - 1;
if (cnt == 1)
        {
        *tpt = *(newpt-1);
        tpt = tpt + 1;
        strcpy(tpt, ".r");
        }
if (cnt == 2)
        {
        *tpt = *(newpt-2);
        *(tpt+1) = *(newpt-1);
        tpt = tpt + 2;
        strcpy(tpt, ".r");
        }
if (cnt == 3)
        {
        *tpt = *(newpt-2);
        *(tpt+1) = *(newpt-1);
        *(tpt+2) = *(newpt-2);
```

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```
                tpt = tpt + 3;
                strcpy(tpt, ".r");
                }
        strcpy(filename2, filename1);
        tpt = strchr(filename2,'.');
        strcpy(tpt, ".vol");

       cnt = 0;
       ac = &data_array[0][0];


        i = i - 1;
        Mark_breaths(i);
        Calculate_work(i);
        Press_time_integral(i);

        fcloseall;
}

/*****************************************************************
*****/
void
Mark_breaths(int cntb)
{
int cnti = 1, cnte = 0;

breath[0][1] = 1;
breath[0][0] = 1;

for (cnti=1; cnti < cntb; ++cnti)
        {
        if ((data_array[cnti][1] == 0) && (cnti > 3))
                {
                breath[cnti][0] = 0;
```

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```
                if (data_array[cnti-1][1] > 0)
                        {
                        breath[cnti][1] = breath[cnti-1][1] + 1;
                        }
                else breath[cnti][1] = breath[cnti-1][1];
                }
        if ((data_array[cnti][1] == 0) && (cnti < 3))
                {
                breath[cnti][0] = 1;
                breath[cnti][1] = 1;
                }
        if (data_array[cnti][1] > 0)
                {
                breath[cnti][0] = 2;
                breath[cnti][1] = breath[cnti-1][1];
                }
        if (data_array[cnti][1] < 0)
                {
                breath[cnti][0] = 1;
                breath[cnti][1] = breath[cnti-1][1];
                }
        }
}
/*****************************************************************
*****/
void
Calculate_work(int cnta)
{
float vol[ROWMAX];
float ip[MAXBREATHS], ep[MAXBREATHS];
float a1, a2, a3, area1 = 0.0, area2 = 0.0;
float  areall[20], areall1[20], areall2[20];
int acnt = 1, expcnt, cnt = 0, mark;
int max, b = 1, breaths;
```

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```
float min=0.0, great, least;
float ave_area = 0.0, ave_area1 = 0.0, ave_area2 = 0.0,
    mean_area, mean_area1, mean_area2,
    var, var1, var2, vare = 0.0, vare1 = 0.0, vare2 = 0.0,
    varem, varem1, varem2, std_area, std_area1, std_area2,
    sem_area, sem_area1, sem_area2;

printf("CALCULATING WORK OF BREATHING AND WRITING TO %s\n",
filename2);

outfile =  fopen(filename2, "a");  /*open the output file*/

if (outfile == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename2);
        exit(1);
        }

/* for each breath calculate work */
for (acnt = 1; acnt < cnta; ++ acnt)
        {
        switch (breath[acnt][0])
                {
                case 1 :            /* During inspiration */
                        {
                        if (fabs(data_array[acnt][2]) < fabs(data_array[acnt-1][2]))
                                {
                                a1 = fabs(data_array[acnt][3] - data_array[acnt-1][3])
                                    * fabs(data_array[acnt][2]) +
                                    0.5 * fabs(data_array[acnt][3] - data_array[acnt-
1][3])
                                    * fabs(data_array[acnt][2] - data_array[acnt-1][2]);
                                }
                        else
```

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```
                    {
                    a1 = fabs(data_array[acnt][3] - data_array[acnt-1][3])
                        * fabs(data_array[acnt-1][2]) +
                        0.5 * fabs(data_array[acnt][3] - data_array[acnt-
1][3])
                        * fabs(data_array[acnt][2] - data_array[acnt-1][2]);

                    }
                if (data_array[acnt][2] > 0) area1 = area1 - a1;
                   else area1 = area1 + a1;
                break;
                }
            case 2 :
                {
                if (fabs(data_array[acnt][2]) < fabs(data_array[acnt-1][2]))
                    {
                    a2 = fabs(data_array[acnt][3] - data_array[acnt-1][3])
                        * fabs(data_array[acnt][2]) +
                        0.5 * fabs(data_array[acnt][3] - data_array[acnt-
1][3])
                        * fabs(data_array[acnt][2] - data_array[acnt-1][2]);
                    }
                else
                    {
                    a2 = fabs(data_array[acnt][3] - data_array[acnt-1][3])
                        * fabs(data_array[acnt-1][2]) +
                        0.5 * fabs(data_array[acnt][3] - data_array[acnt-
1][3])
                        * fabs(data_array[acnt][2] - data_array[acnt-1][2]);
                    }
                if (data_array[acnt][2] < 0) area2 = area2 - a2;
                   else area2 = area2 + a2;
                break;
                }
```

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```
                case 0 :
                /* when value calculated place into array */
                        {
                        if (breath[acnt-1][0] == 2)
                                {
                                areall[b] = fabs(area1 + area2);
                                areall2[b] = area2;
                                ++b;
                                area1 = 0.0;
                                area2 = 0.0;
                                break;
                                }
                        else
                                {
                                a1 = fabs(data_array[acnt][3] - data_array[acnt-1][3])
                                    * fabs(data_array[acnt][2]) +
                                    0.5 * fabs(data_array[acnt][3] - data_array[acnt-
1][3])
                                    * fabs(data_array[acnt][2] - data_array[acnt-1][2]);
                                area1 = area1 + a1;
                                areall1[b] = area1;
                                break;
                                }
                        }
                }
        }
b = b - 1;
for (ave = 1; ave <= b; ++ ave)
        {
        ave_area = ave_area + areall[ave];
        ave_area1 = ave_area1 + areall1[ave];
        ave_area2 = ave_area2 + areall2[ave];
        }
mean_area = ave_area / b;
```

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```
mean_area1 = ave_area1 / b;
mean_area2 = ave_area2 / b;
/* printf("AREA     SEM      STD      IAREA    ISEM     ISTD     EAREA    ESEM
ESTD   PT INT    STD      SEM      \n");   */
/* fprintf(outfile, "AREA     SEM      STD      PT INT    STD      SEM      \n"); */
fprintf(outfile, " %8.3f ", mean_area);
/* printf("%8.3f ", mean_area); */

if (b == 1)
        {
        fprintf(outfile, "ONLY ONE BREATH     ");
        printf("ONLY ONE BREATH     ");
        }
else
        {
        for (ave = 1; ave <= b; ++ ave)
                {
                var = mean_area - areall[ave];
                var1 = mean_area1 - areall1[ave];
                var2 = mean_area2 - areall2[ave];
                varem = var * var;
                varem1 = var1 * var1;
                varem2 = var2 * var2;
                vare = vare + varem;
                vare1 = vare1 + varem1;
                vare2 = vare2 + varem2;
                }
        vare = vare / b;
        vare1 = vare1 / b;
        vare2 = vare2 / b;
        std_area = sqrt(vare);
        std_area1 = sqrt(vare1);
        std_area2 = sqrt(vare2);
        sem_area = std_area / (sqrt(b - 1));
```

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```
        sem_area1 = std_area1 / (sqrt(b - 1));
        sem_area2 = std_area2 / (sqrt(b - 1));
        printf("%8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f",
             mean_area, std_area, sem_area, mean_area1, std_area1, sem_area1,
             mean_area2, std_area2, sem_area2);
        fprintf(outfile, "%8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f %8.3f  ",
             std_area, sem_area, mean_area1, std_area1, sem_area1,
             mean_area2, std_area2, sem_area2);
        }
}
/*****************************************************************
*****/
void
Press_time_integral(int pt)

{
float pt_area[MAXBREATHS][3];
float pta = 0.0, area,  mpta = 0.0,  mptai = 0.0, mptae = 0.0,
    stdpta, stdpta1, stdpta2, sempta, sempta1, sempta2,
    var, var1, var2, varem, varem1, varem2, vare = 0.0, vare1 = 0.0, vare2 = 0.0;
float press, time, corrtime = 0.0, timept;
int cntpt, ave = 1, max, ie, a;

/* printf("CALCULATING PRESSURE_TIME INTEGRAL\n");
printf("AND WRITING TO %s \n", filename1); */

for (a = 0; a< MAXBREATHS; ++ a)   /* set array to zero */
        {
        pt_area[a][2] = 0.0;
        pt_area[a][1] = 0.0;
        pt_area[a][0] = 0.0;
        }

for (cntpt = 1; cntpt < pt; ++cntpt)
```

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```
        {
        if (((data_array[cntpt-1][2] < 0) && (data_array[cntpt][2] > 0)) ||
          ((data_array[cntpt-1][2] > 0) && (data_array[cntpt][2] < 0)))
                {
                timept = (fabs(data_array[cntpt-1][2]) *
                        fabs(data_array[cntpt-1][0] - data_array[cntpt][0]))
                        / (fabs(data_array[cntpt-1][2]) + fabs(data_array[cntpt][2]));
                pta = (0.5 * fabs(data_array[cntpt-1][2]) * timept)
                    + (0.5 * fabs(data_array[cntpt][2]) *
                    ((data_array[cntpt][0] - data_array[cntpt-1][0]) - timept));
                }
        else
                {
                if (fabs(data_array[cntpt-1][2]) < fabs(data_array[cntpt][2]))
                pta = fabs(data_array[cntpt-1][2]) * (data_array[cntpt][0] -
data_array[cntpt-1][0])
                    + 0.5 * (fabs(data_array[cntpt][2] - data_array[cntpt-1][2])
                    * (data_array[cntpt][0] - data_array[cntpt-1][0]));
                else
                pta = fabs(data_array[cntpt][2]) * (data_array[cntpt][0] -
data_array[cntpt-1][0])
                    + 0.5 * (fabs(data_array[cntpt][2] - data_array[cntpt-1][2])
                    * (data_array[cntpt][0] - data_array[cntpt-1][0]));
                }

        if (breath[cntpt][0] == 1) ie = 0;  /* this is during inspiration */
        else ie = 1;

        pt_area[ave][ie] = pt_area[ave][ie] + fabs(pta);

        if ((breath[cntpt][0] == 0) && (breath[cntpt-1][0] == 2))
                {
                /* convert from integral of one breath to
                   integral of 1 minute's breathing */
```

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```
                pt_area[ave][2] = pt_area[ave][0] + pt_area[ave][1];
                time = data_array[cntpt][0] - corrtime;
                pt_area[ave][0] = pt_area[ave][0] * (60 / time);
                pt_area[ave][1] = pt_area[ave][1] * (60 / time);
                pt_area[ave][2] = pt_area[ave][2] * (60 / time);
                ++ave;
                pt_area[ave][0] = 0.0;
                pt_area[ave][1] = 0.0;
                pt_area[ave][2] = 0.0;
                corrtime = data_array[cntpt][0];
                }
        }
max = ave - 1;
for (ave = 1; ave <= max; ++ ave)
        {
        mpta = mpta + pt_area[ave][2];
        mptai = mptai + pt_area[ave][0];
        mptae = mptae + pt_area[ave][1];
        }
mpta = mpta / max;
mptai = mptai / max;
mptae = mptae / max;
printf("%8.3f  ", mpta);
fprintf(outfile, "%8.3f  ", mpta);

if (max == 1)
        {
        fprintf(outfile, "ONLY ONE BREATH     ");
        printf("ONLY ONE BREATH     ");
        }
else
        {
        for (ave = 1; ave <= max; ++ ave)
```

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```
                {
                var = mpta - pt_area[ave][2];
                var1 = mptai - pt_area[ave][0];
                var2 = mptae - pt_area[ave][1];
                var = var * var;
                var1 = var1 * var1;
                var2 = var2 * var2;
                vare = vare + var;
                vare1 = vare1 + var1;
                vare2 = vare2 + var2;
                }
        vare = vare / max;
        vare1 = vare1 / max;
        vare2 = vare2 / max;
        stdpta = sqrt(vare);
        stdpta1 = sqrt(vare1);
        stdpta2 = sqrt(vare2);
        sempta = stdpta / (sqrt(max - 1));
        sempta1 = stdpta1 / (sqrt(max - 1));
        sempta2 = stdpta2 / (sqrt(max - 1));
        printf("%8.3f  %8.3f  ", stdpta, sempta);
        fprintf(outfile, "%8.3f  %8.3f  ", stdpta, sempta);
        printf("%8.3f  %8.3f  %8.3f  ", mptai, stdpta1, sempta1);
        fprintf(outfile, "%8.3f  %8.3f  %8.3f  ", mptai, stdpta1, sempta1);
        printf("%8.3f  %8.3f  %8.3f  ", mptae, stdpta2, sempta2);
        fprintf(outfile, "%8.3f  %8.3f  %8.3f  ", mptae, stdpta2, sempta2);
        }
fclose(outfile);
}
/*************************************************************************
*****/
```

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Appendix 4.7 Programme to correct the time base and assess I:E ratio and calculate dynamic compliance (Newctim)

```
/* PROGRAMME TO CORRECT TIME BASE,
 * ASSESS I/E RATIO AND CALCULATE DYNAMIC COMPLIANCE
 * reads from .*r
 * corrects the time base
 * writes IE data to *.vol
 * */



#include <stdio.h>
#include <stdlib.h>
#include <math.h>
#include <string.h>

#define ROWMAX 700
#define COLMAX 7
#define MAXBREATHS 10
#define VERSION "version 3.01"

float data_array[ROWMAX][COLMAX];
float mean_array[MAXBREATHS][2];
char pathname[30] = "fileinfo", pathname1[30], pathname2[30], filename[30];
char *answer, *answer1;
int cnt = 0,i=0, ave, out, check=0;
int breath[ROWMAX][3];
FILE *fp, *fp1, *fp2, *fo;
float a,b;
float *ac, *acc[COLMAX];
int result, info, numfiles;

void Define_breaths(int);
```

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```
void Compute_compliance(int);
void Correct_breath_time(int);

main(void)
{
        int num_means;

printf("\n\n PROGRAMME TO CORRECT \n TIME BASE, ASSESS I/E RATIO \n
\t%s\n", VERSION);
        fo = fopen(pathname, "r");

        if (fo == NULL)
                {
                printf("UNABLE TO OPEN FILEINFO");
                exit(1);
                }
        info = fscanf(fo, "%s %s %s %s %s %s", filename, filename, filename,
pathname1, pathname1, pathname2);

        ac = &data_array[0][0];

        fp = fopen(filename, "r");  /*open the input file*/

        if (fp == NULL)
                {
                printf("UNABLE TO OPEN %s\n", filename);
                exit(1);
                }
         printf("READING THE DATA FROM: %s\n", filename);
         while ((i++ <= ROWMAX) && (!feof(fp)))
                 {
                 result = fscanf(fp, "%f %f %f %f %f %f %f\n",
                                        &data_array[i][0],
                                        &data_array[i][1],
```

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```
                                        &data_array[i][2],
                                        &data_array[i][3],
                                        &data_array[i][4],
                                        &data_array[i][5],
                                        &data_array[i][6]);

                }
        fclose(fp);
        i = i - 1;
        Define_breaths(i);
        i = i - 1;
        Compute_compliance(i);
        Correct_breath_time(i-1);
}
/*****************************************************************************
******/
void
Define_breaths(int count)
{
int acount=0,bc = 0;

    /* breath[acount][0] will be 0 if flow 0, 1 if inspiration,
                        * 2 if expiration */
    /* breath[acount][1] will be breath number */

breath[acount][1] = 1;
breath[acount][0] = 1;
for(acount = 1; acount < count; ++acount)
        {
        if ((data_array[acount][1] == 0) && (acount > 2))
                {
                switch(breath[acount-1][0])
                        {
                        case 1:
```

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```
                        breath[acount][0] = 0;
                        breath[acount+1][0] = 2;
                        breath[acount][1] = breath[acount-1][1];
                        breath[acount+1][1] = breath[acount][1];
                        break;
                case 2:
                        breath[acount][0] = 0;
                        breath[acount+1][0] = 1;
                        breath[acount][1] = breath[acount-1][1] + 1;
                        breath[acount+1][1] = breath[acount][1];
                        break;
                }
            ++acount;
            }
        else
            {
            breath[acount][0] = breath[acount-1][0];
            breath[acount][1] = breath[acount-1][1];
            }
        }
}
/*****************************************************************
*****/
void
Compute_compliance(int cntco)

{
int ccount, co = 0, com;
FILE *tfile, *t1file;
char timefile[30], time1file[30];
char *tpt;
float compl, vol, vole = 0.0, comple = 0.0, compli, tcomp = 0.0, mcomp, semin,
    varcomp, varecomp, sdin = 0.0;
float ave_comp[MAXBREATHS];
```

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```
printf("COMPUTING THE COMPLIANCE FOR EACH BREATH\n");

strcpy(timefile, filename);
tpt = strchr(timefile, '.');
*tpt = *(tpt + 1);
strcpy(tpt+1, ".vol");
strcpy(time1file, timefile);

tfile = fopen(timefile, "w");

for (ccount = 1; ccount < cntco; ++ccount)
        {
        if ((breath[ccount][0] == 0) && (breath[ccount-1][0] == 1))
                {
                compl = fabs(data_array[ccount][2] - comple);
                vol = fabs(data_array[ccount][3] - vole);
                compli = (vol / compl) / 1000;    /* converts to litres from ml) */
                ave_comp[co] = compli;
                co += 1;
                }
        if ((breath[ccount][0] == 0) && (breath[ccount-1][0] == 2))
                {
                vole = data_array[ccount][3];
                comple = data_array[ccount][2];
                }
        }
for (com = 0; com < co; ++com)
        {
        tcomp += ave_comp[com];
        }
mcomp = tcomp / co;

for (com = 0; com < co; ++com)
```

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```
        {
        sdin = sdin + ((mcomp - ave_comp[com]) * (mcomp - ave_comp[com]));
        }
sdin = sqrt(sdin/co);
semin = sdin/(sqrt(co));

fprintf(tfile, "%8.5f  %8.5f  %8.5f  ", mcomp, sdin, semin);

fclose(tfile);

}
/*****************************************************************
*****/
void
Correct_breath_time(int cntt)

{
float temp = 0.0, corr = 0.0, insp = 0.0, exp = 0.0, ratio;
float minsp = 0.0, sdin = 0.0, mexp = 0.0, sdexp = 0.0, semin, semexp;
int tcount = 0, t = 0;
float time[2][20];
int tt, to, ti = 0, te = 0;
FILE *tfile, *t1file;
char timefile[30], time1file[30];
char *tpt;

printf("CORRECTING THE TIME BASE OF EACH BREATH\n");

strcpy(timefile, filename);
tpt = strchr(timefile, '.');
*tpt = *(tpt + 1);
strcpy(tpt+1, ".vol");
strcpy(time1file, timefile);
tpt = strchr(time1file, '.');
```

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```
strcpy(tpt, ".t");

tfile = fopen(timefile, "a");
/* t1file = fopen(time1file, "w");    */

for (tcount = 1; tcount < cntt; ++tcount)
        {
        data_array[tcount][0] = data_array[tcount][0] - temp;
        if (breath[tcount+1][0] == 0)
                temp = data_array[tcount+1][0];
        }
for (tcount = 1; tcount < cntt; ++tcount)
        {
        if (breath[tcount+1][0] == 0)
                {
                time[0][t] = breath[tcount][0];
                time[1][t] = data_array[tcount][0];
                t += 1;
                }
        }

for (to = 0; to < t; ++to)
        {
        if (time[0][to] == 1)
                {
                insp += time[1][to];
                ti += 1;
                }
        }
minsp = insp / ti;
ti = 0;
for (to = 0; to < t; ++to)
        {
        if (time[0][to] == 1)
```

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```
                {
                sdin = sdin + ((minsp - time[1][to])*(minsp - time[1][to]));
                ti += 1;
                }
        }
sdin = sqrt(sdin/ti);
semin = sdin/(sqrt(ti));

for (to = 0; to < t; ++to)
        {
        if (time[0][to] == 2)
                {
                exp += time[1][to];
                te += 1;
                }
        }
mexp = exp / te;
te = 0;
for (to = 0; to < t; ++to)
        {
        if (time[0][to] == 2)
                {
                sdexp = sdexp + (mexp - time[1][to])*(mexp - time[1][to]);
                te += 1;
                }
        }
sdexp = sqrt(sdexp/te);
semexp = sdexp/(sqrt(te));
ratio = minsp / mexp;

fprintf(tfile, "%f\t %f\t %f\t %f\t %f", minsp, semin, mexp, semexp, ratio);

fclose(tfile);
}
```

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```
/*****************************************************************
*****/
```

Appendix 4.8 Programme to calculate flow volume parameters for several breaths (Newfv3)

```
/* PROGRAMME TO CALCULATE FLOW VOLUME PARAMETERS
 * FOR SEVERAL BREATHS (from the .r file input)
 * this version read files containing the resistance not corrected for elastic recoid pressure
 * output is to .*vol  */



#include <c:\#prog\qc2\include\stdio.h>
#include <c:\#prog\qc2\include\stdlib.h>
#include <c:\#prog\qc2\include\math.h>
#include <c:\#prog\qc2\include\string.h>

#define ROWMAX 700
#define COLMAX 7
#define MAXBREATHS 10
#define VERSION "version 1.1"

float data_array[ROWMAX][COLMAX];
float mean_array[MAXBREATHS][2], calc_array[MAXBREATHS][10];
char pathname[30] = "fileinfo", filename[30], filename1[30], filename2[30];
char *answer, *answer1;
int cnt = 0, i=0, ave, out, check=0;
int b;
int breath[ROWMAX][3];
FILE *fp, *outfile, *outfile1, *fp2, *fo;
float *ac, *acc[COLMAX];
int result, info;
char *name, *newname, *newname1, *tm;

void Mark_breaths(int);
```

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```
void Average_values(int);
void Correct_vol(int);
void Fill_data(int);
void Calc_area(int);

main(void)
{
        int num_means;

        printf("\n\n PROGRAMME TO ANALYZE FLOW VOLUME CURVES
\n");
        printf("\t\t %s\n", VERSION);
/*      puts("PLEASE ENTER THE NAME OF THE DATA FILE: ");
        scanf("%s", filename);
        puts("PLEASE ENTER THE NAME OF THE OUTPUT FILE: ");
        scanf("%s", filename1);
        puts("PLEASE ENTER THE NAME OF THE SUMMARY FILE: ");
        scanf("%s", filename2); */

        fo = fopen(pathname, "r");

        if (fo == NULL){
            printf("UNABLE TO OPEN FILEINFO");
            exit(1);
            }
  /*    info = fscanf(fo, "%s %s %s %s %s %s", filename, filename, filename,
filename1, filename1, filename1); */

        info = fscanf(fo, "%s", filename);    /* use this version when want single file
input */

        ac = &data_array[0][0];

        fp = fopen(filename, "r");  /*open the input file*/
```

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```
if (fp == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename);
        exit(1);
        }
 printf("READING THE DATA FROM: %s\n", filename);
 while ((i++ <= ROWMAX) && (!feof(fp)))
        {
         result = fscanf(fp, "%f %f %f %f %f %f \n",
                                &data_array[i][0],
                                &data_array[i][1],
                                &data_array[i][2],
                                &data_array[i][3],
                                &data_array[i][4],
                                &data_array[i][5],
                                &data_array[i][6]);
         }

strcpy(filename1, filename);
name = strchr(filename1, '.');
newname = strrchr(filename1, 'r');
cnt = fabs(name - newname);
if (cnt == 2)
        {
        *name = *(name+1);
        strcpy(name+1, ".vol");
        }
if (cnt == 3)
        {
        *name = *(name+1);
        *(name+1) = *(newname-1);
        strcpy(name+2, ".vol");
        }
```

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```
        if (cnt == 4)
                {
                *name = *(name+1);
                *(name+1) = *(newname-2);
                strcpy(name+3, ".vol");
                }

        strcpy(filename2, filename1);
        name = strchr(filename2, '.');
        strcpy(name + 1,"vol");

         Mark_breaths(i);
         Calc_area(i);
         Correct_vol(i);
          Fill_data(i);
         Average_values(i);

         fcloseall;
}
/*****************************************************************
*****/
void
Mark_breaths(int cntb)
{
int cnti = 1, cnte = 0;

breath[0][1] = 1;
breath[0][0] = 1;
for (cnti=1; cnti < cntb; ++cnti)
        {
        if ((data_array[cnti][1] == 0) && (cnti > 3))
                {
                breath[cnti][0] = 0;
                if (data_array[cnti-1][1] > 0)
```

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```
                    {
                    breath[cnti][1] = breath[cnti-1][1] + 1;
                    }
            else breath[cnti][1] = breath[cnti-1][1];
            }
        if ((data_array[cnti][1] == 0) && (cnti < 3))
            {
            breath[cnti][0] = 1;
            breath[cnti][1] = 1;
            }
        if (data_array[cnti][1] > 0)
            {
            breath[cnti][0] = 2;
            breath[cnti][1] = breath[cnti-1][1];
            }
        if (data_array[cnti][1] < 0)
            {
            breath[cnti][0] = 1;
            breath[cnti][1] = breath[cnti-1][1];
            }
        }
}

/*****************************************************************
*****/
void
Calc_area(int cnta)

{
int a, in = 0, ind, br;
float sarea, tarea, area, mean;
float var = 0, vare, varem;
float area_array[MAXBREATHS];
```

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```
printf("AVERAGING VALUES\n AND WRITING TO %s\n", filename2);

outfile =  fopen(filename2, "a");  /*open the output file*/

if (outfile == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename2);
        exit(1);
        }


for(a=0; a<=MAXBREATHS; ++a) area_array[a] = 0;

for(a=1; a<=cnta; ++a)
        {
        if ((breath[a][0] == 0) && (breath[a+1][1] != breath[a-1][1])
            && (breath[a+1][1] != 0))
                {
                ++in;
                sarea = fabs((data_array[a][3] - data_array[a-1][3]) *
                                data_array[a-1][1]);
                tarea = 0.5 * fabs((data_array[a][3] - data_array[a-1][3]) *
                                (data_array[a][1] - data_array[a-1][1]));
                area = sarea + tarea;
                area_array[in] = area_array[in] + area;
                }
        else
                {
                sarea = fabs((data_array[a][3] - data_array[a-1][3]) *
                                data_array[a-1][1]);
                tarea = 0.5 * fabs((data_array[a][3] - data_array[a-1][3]) *
                                (data_array[a][1] - data_array[a-1][1]));
                area = sarea + tarea;
                area_array[in] = area_array[in] + area;
```

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```
                }

        }
in = in - 1;
area = 0;
for (a=0; a<=in; ++a)
        {
        area = area + area_array[a];
        }
mean = area / a;
for(br=0;br<= in;++br)
        {
        vare = mean - area_array[br];
        vare = vare * vare;
        var = var + vare;
        }
var = var / a;
var = sqrt(var);
varem = var / sqrt(br);
fprintf (outfile, " %8.3f\t  %8.3f\t %8.3f\t",
                                mean,
                                var,
                                varem);

}
/*************************************************************************
*****/
void
Correct_vol(int cntv) /* read through each breath and zero
                        volumes and times for each breath */
{
int v;
float  vole = 0.0, voli = 0.0, ti = 0.0, te = 0.0;
```

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```
for (v=1; v<cntv; ++v)
        {
        switch (breath[v][0])
                {
                case 0:      /* point of zero flow */
                        {
                        if (breath[v+1][0] == 1)   /*ie end of expiration */
                                {
                                voli = data_array[v][3];
                                te = data_array[v][0];
                                data_array[v][3] = data_array[v][3] - vole;
                                data_array[v][0] = data_array[v][0] - ti;
                                vole = 0.0;
                                ti = 0.0;
                                break;
                                }
                        else                    /*ie end of inspiration */
                                {
                                vole = data_array[v][3];
                                ti = data_array[v][0];
                                data_array[v][3] = data_array[v][3] - voli;
                                data_array[v][0] = data_array[v][0] - te;
                                te = 0.0;
                                voli = 0.0;
                                break;
                                }
                        }
                case 1:                         /*ie inspiration */
                        {
                        data_array[v][3] = data_array[v][3] - voli;
                        data_array[v][0] = data_array[v][0] - te;
                        break;
                        }
                case 2:
```

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```
                    {
                    data_array[v][3] = data_array[v][3] - vole;
                    data_array[v][0] = data_array[v][0] - ti;
                    break;
                    }
                }
        }
}
/*****************************************************************
*****/
void
Fill_data(int cntd)

{
int c = 0;
float vol=0.0, te = 0.0, ti = 0.0, vi = 0.0, ve = 0.0, fmax = 0.0;
float vole = 0.0, voli = 0.0;
float volpi = 0.0, tpi = 0.0, volpe = 0.0, tpe = 0.0;

b = 0;
for (c = 1; c < cntd; ++c)
        {
        switch (breath[c][0])
                {
                case 0:
                    {
                        if (breath[c+1][0] == 1)  /* ie end of expiration */
                                {
                                vol = fabs(data_array[c][3]);
                                calc_array[b][5] = vol; /* expiratory volume */
                                calc_array[b][6] = fabs(volpe);
                                calc_array[b][7] = fabs(volpe * 100 / calc_array[b][5]);
                                calc_array[b][8] = tpe;
                                calc_array[b][9] = tpe * 100 / data_array[c-1][0];
```

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```
                tpe = 0.0;
                voli = 0.0;
                volpe = 0.0;
                b = b + 1;
                fmax = 0;
                break;
                }
        else
                {               /* end of inspiration */

                vol = fabs(data_array[c][3]);
                calc_array[b][0] = vol; /* inspiratory volume */
                calc_array[b][1] = fabs(volpi);
                calc_array[b][2] = fabs(volpi * 100 / calc_array[b][0]);
                calc_array[b][3] = tpi;
                calc_array[b][4] = tpi * 100 / data_array[c-1][0];
                tpi = 0.0;
                volpi = 0.0;
                vole = 0.0;
                fmax = 0;
                break;
                }
        }
case 1:         /* during inspiration */
        {
        if (data_array[c][1] < fmax)
                {
                fmax = data_array[c][1];
                tpi = data_array[c][0];
                volpi = data_array[c][3];
                break;
                }
        else break;
        }
```

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```
                case 2:
                        {
                        if (data_array[c][1] > fmax)
                                {
                                fmax = data_array[c][1];
                                tpe = data_array[c][0];
                                volpe = data_array[c][3];
                                break;
                                }
                        else break;
                        }
                }
        }
}

/*****************************************************************************
*****/
void
Average_values(int cnta)
{
float tim;
int ind, br = 0, nat, tan;
float max=0.0, min=0.0, great, least;
float var, ave, vare, sum, varem;
float var_array[10], mean_array[10], ave_array[10], varem_array[10];

printf("AVERAGING VALUES\n AND WRITING TO %s\n", filename1);

outfile =  fopen(filename1, "a");  /*open the output file*/

if (outfile == NULL)
        {
        printf("UNABLE TO OPEN %s\n", filename1);
        exit(1);
```

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```
        }

for(ind=0;ind<=9;++ind)
        {
        sum = 0.0;
        for(br=0;br<b;++br) sum = calc_array[br][ind] + sum;
        ave = sum/br;
        ave_array[ind] = ave;
        }
for(ind=0;ind<=9;++ind)
        {
        var = 0.0;
        for(br=0;br<b;++br)
                {
                vare = calc_array[br][ind] - ave_array[ind];
                vare = vare * vare;
                var = var + vare;
                }
        var = var / br;
        var_array[ind] = sqrt(var);
        varem = var_array[ind] / sqrt(br);
        varem_array[ind] = varem;
        if ((ind == 2) || (ind == 4) || (ind == 7) || (ind == 9))
                {
                fprintf (outfile, " %8.3f\t  %8.3f\t %8.3f\t",
                                ave_array[ind],
                                var_array[ind],
                                varem_array[ind]);
                }
        }
}
 /*****************************************************************
```

The end.

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